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Splenoportography: A Valuable Adjunct in the Study of Portal Hypertension. By HECTOR F. RODRIGUEZ, M.D., FRANK H. GARDNER, M.D., and RAFAEL DIAZ-BONNET, M.D. 1

Quantitation of the Activity of Rheumatoid Arthritis. 2. Recession of Morning Stiffness as Patients Go into Remission. By JOHN LANSBURY, M.D. 8

Quantitation of the Activity of Rheumatoid Arthritis. 3. The Maximum 5-Minute Cutler Sedimentation Rate as an Index. By JOHN LANSBURY, M.D. 12

The Lack of Effect of Ingested Ferrous Sulfate on the Guaiac Test for Occult Blood in the Stool. By JOHN COLLINS HARVEY, M.D. 17

The Treated Pulmonary Lesion and Its Tubercle Bacillus. I. Pathology and Pathogenesis. By WILLIAM E. LORING, M.D., and H. MACVANDIVIERE, M.A. 20

The Treated Pulmonary Lesion and Its Tubercle Bacillus. II. The Death and Resurrection. By H. MAC VANDIVIERE, M.A., WILLIAM E. LORING, M.D., IRENE MELVIN, M.A., and STUART WILLIS, M.D. 30

The Serum Aldolase Level in Acute Myocardial Infarction. By BRUNO W. VOLK, M.D., SAMUEL LOSNER, M.D., STANLEY M. ARONSON, M.D., and HERBERT LEW, B.S. 38

Clearance of Radioactive Iodine from the Lower Extremities of Patients with Myocardial Infarction. By FRANZ K. BAUER, M.D., FREDERICK R. MUGLER, JR., M.D., VERNON W. LIEBERMAN, M.D., and JOHN P. WESTERGART, M.D. 44

Diagnostic and Prognostic Significance of Eosinopenia in Acute Myocardial Infarction. By KNUT KIRKEBY, M.D. 50

The Cough Response of Normal Human Subjects Stimulated Experimentally by Citric Acid Aerosol: Alterations Produced by Antitussive Agents. Part I: Methology. By HYLAN A. BICKERMAN, M.D., BURTON M. COHEN, M.D., and ELAINE GERMAN, M.D. 57

An Evaluation of the Single Breath Technique for Measuring Anatomic Respiratory Dead Space with the Nitrogen Meter. By RUSSELL H. WILSON, M.D., PH.D., BRUCE E. JAY, B.S., PAUL L. RICHBURG, M.D., and ROBERT EVANS, PH.D. 67

Apparent Renal Defect in Sicklemic Individuals. By CHRIS J. D. ZARAFONETIS, M.D., JOHN D. MCMASTER, M.D., LYNDALL MOLTHAN, M.D., and WILLIAM A. STEIGER, M.D. 76

Electrophoretic Studies in Disseminated and Fixed Lupus Erythematosus. By LUIS BAPTISTA, M.D., GUNTER HOXTER, LINO VELLINI and RAUL MUNGIOLI. 83

Progress of Medical Science

Medicine—The Problem of the Volume Component of Body Fluid Homeostasis. By E. H. BRESLER, M.D. 93

Neurology and Psychiatry—Tension Headache: A Review. By FRANK R. DRAKE, M.D. 105

Physiology—Proceedings of the Physiological Society of Philadelphia, March 20, 1956. 113

Book Reviews and Notices. 116

Complete contents on adv. page 8

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JULY, 1956

ORIGINAL ARTICLES

SPLENOPORTOGRAPHY: A VALUABLE ADJUNCT IN THE STUDY OF PORTAL HYPERTENSION

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Recent reports[1,2,4] have emphasized the value of outlining the splenic and portal veins radiologically by percutaneous injection of radiopaque material into the spleen. This procedure has the advantage of defining types and degrees of portal hypertension before laparotomy. Splenic portography is specially valuable in Puerto Rico, where schistosomiasis (Manson) of the liver leads often to portal hypertension[6], with the development of huge splenic enlargement and esophageal varices. As these patients may show marked portal hypertension with mild to moderate impairment of liver function, they are ideally suited for shunt surgery. We have found that in these cases, splenic portography is a relatively simple procedure and one which yields valuable information. At present, this method is being routinely employed in all subjects with portal hypertension who are to undergo surgery at the Bayamon District Hospital, Bayamon, Puerto Rico.

Technique: After previously performing an intravenous test to exclude sensitivity to iodopyracet* (Diodrast) the injection site was infiltrated with 1% tetracaine hydrochloride to the peritoneal surface. No sedation or analgesic was given to the patient. When splenomegaly was present, the radiopaque material was injected into the spleen with a 3-inch, 18-gauge needle at the anterior axillary line below the costal margin in the left upper quadrant. The patient was instructed to hold his breath and the long needle was thrust cephalad and medially at an approximately 45° angle from the entrance site. If the spleen was only slightly enlarged, the Diodrast was injected by puncturing the spleen through the left ninth intercostal space in the midaxillary line. As the needle was pushed through the skin, usually a firm re-

*We are indebted to Dr. H. Scribner, Winthrop-Stearns, Inc., for providing part of the Diodrast used in this study.

sistance was felt to indicate penetration of the spleen. Efforts were then made to aspirate blood through the needle into a 30-ml. syringe which contains 20 to 30 ml. of Diodrast (70% concentration). As experience was obtained, blood was only infrequently aspirated. The absence of blood does not indicate an unsuccessful splenic puncture. The contrast medium is injected rapidly, usually requiring 3 to 5 seconds. As the last 5 ml. of Diodrast is injected, an anterior-posterior film is taken with the routine Roentgen technique for a plain film of the abdomen.

TABLE 1.—RESULTS OF SPLENOPORTOGRAPHY

Diagnosis	*Number Studied*	*Average Diameter*		*General Description*
		S.V.	*P.V.*	
1. Normal	2	0.65	0.8	Splenic and portal veins with smooth course. Intrahepatic branches well visualized. Collateral vessels not seen.
2. Splenomegaly without portal hypertension	4	0.9	1.3	Splenic vein elongated but of normal caliber. Portal vein somewhat wider. Intrahepatic branches well visualized. Collateral vessels not seen.
3. Bilharzial cirrhosis	10	1.65	2.3	Splenic and portal veins dilated and tortuous. Varices seen in two cases, coronary vein in one, other collaterals in two. Intrahepatic branches not seen clearly.
4. Bilharzial and alcoholic cirrhosis	3	1.7	2.2	Very similar to 3. Varices seen in one case. Veins dilated and tortuous.
5. Portal cirrhosis	6	1.4	1.9	Splenic and portal veins not as dilated as in 3 and 4. Esophagus varices visualized in two cases. Intrahepatic branches poorly visualized.
6. Extrahepatic obstruction; portal vein thrombosis	1	1.2	Not visualized	Splenic vein slightly wider than normal, portal vein not visualized. Esophageal varices seen. A large omental vein crossed the abdomen and connected the splenic vein, through collateral branches, to the inferior vena cava.

Results. Twenty-eight successful splenoportograms have been done in 35 procedures (80%). Successful studies were available in 26 of 30 patients (two had repeated procedures postoperatively). Three cases of initial failures had successful punctures subsequently. In 4 patients no visualization was obtained. Two patients with normal-sized spleen, 4 with splenomegaly but without portal hypertension, and 20 with splenomegaly and portal hypertension were evaluated by this procedure. The diagnosis of the respective groups are tabulated in Table 1.

NORMAL VENOGRAPHY. In the patients examined without portal hypertension, the radiopaque material promptly leaves the spleen with visualization of the splenic and portal veins and the intrahepatic branches. The splenic vein characteristically has a smooth outline (Fig. 1). In these 6 patients the splenic vein had a diameter of 0.6 cm. to 0.8 cm., while the portal vein ranged from 1.0 to 1.5 cm. No collateral branches from the splenic vein or filling of the mesenteric veins were visualized. A residual amount of radiopaque material remains in the spleen, clearing gradually in 6 to 12 hours.

PORTAL HYPERTENSION. (See Fig. 2). Injection shows splenic and portal veins which are wider than those of patients without hypertension. The splenic vein is more tortuous in its course, and the hepatic vein tributaries do not visualize completely. The in-

complete filling of the venous radicles in the liver probably indicates obstruction to the rate of portal blood flow. Collateral tributary veins often are visualized. In 6 patients among the 22 studied with portal hypertension, collateral veins consistent with esophageal varices were demonstrated. Esophageal films after swallowing a standard barium meal, or esophagoscopy, or both, revealed varices in 10 patients. However, in one patient esophagoscopy and barium contrast films were normal, while venography clearly outlined varices (Fig. 3). In another patient splenoportography established the presence of varices, although the barium swallow film was normal.

EXTRAHEPATIC OBSTRUCTION. This procedure was helpful in understanding extrahepatic portal hypertension. Normal liver function tests associated with splenomegaly and esophageal varices are frequently observed in patients with *Schistosoma mansoni* infestation of the liver. Since stool examinations and rectal biopsies may not yield evidence of this blood fluke, splenic venography may be an aid to exclude extrahepatic obstruction from other sources in a population with a high incidence of bilharzia. Splenic venography definitely

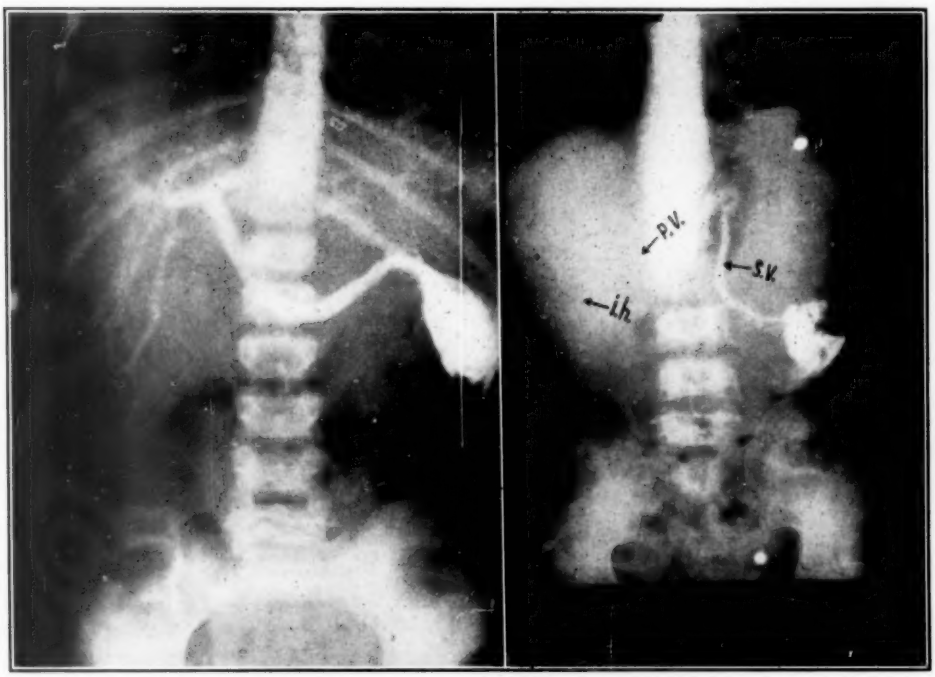

Fig. 1.—Normal. *Left*, a 15-year-old patient with schistosomiasis and hepatomegaly, but without splenomegaly or esophageal varices. Splenic venography shows splenic and portal veins of normal caliber. The intrahepatic branches are clearly outlined, denoting no obstruction to the rate of portal blood flow. ***Right***, a case of splenomegaly due to chronic myelogenous leukemia, also showing veins of normal caliber (s.v. = splenic vein; p.v. = portal vein; i.h. = intrahepatic branches). No collaterals are identified and the course of the venous flow is smooth.

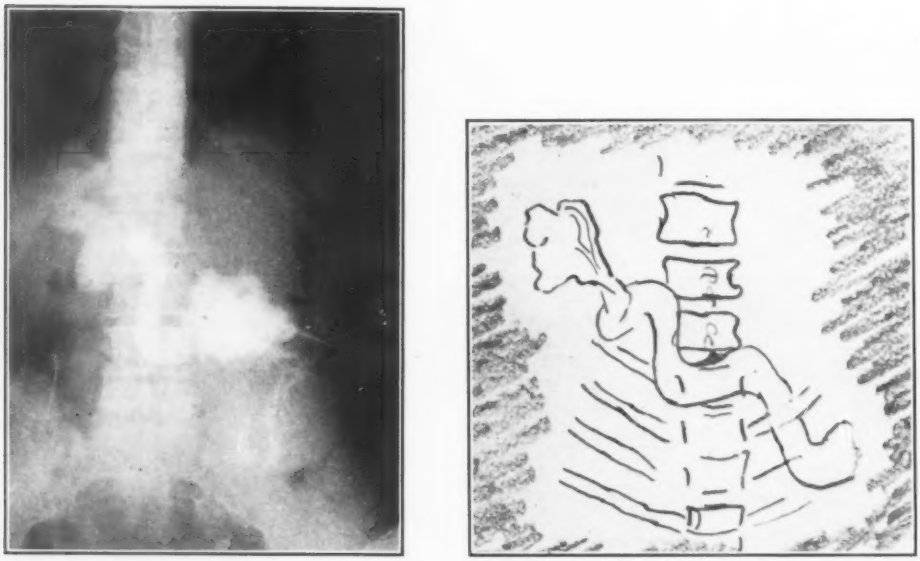

Fig. 2.—Portal Hypertension. Cases with increased pressure in the portal venous system due to intrahepatic obstruction. *Left,* a case of bilharzial cirrhosis. *Right,* a patient with alcoholic cirrhosis. The splenic and portal veins are greatly distended and tortuous. The intrahepatic branches are not clearly seen, suggesting intrahepatic obstruction.

Fig. 3.—Varices. A female patient, aged 35, with cirrhosis of the liver. Barium swallow and esophagoscopy failed to disclose the presence of varices. Splenoportography indicates some increase in the caliber of splenic (s.v.) and portal (p.v.) veins, and clearly shows a cluster of gastroesophageal varices (g.v.) arising from the coronary vein.

demonstrates the presence of portal vein thrombosis, as shown in Fig. 4, a finding which was verified at the time of surgical exploration.

PORTOCAVAL ANASTOMOSIS. Portal venography was used to evaluate the patency of a vascular shunt in one patient. The usefulness of the procedure in following the patient postoperatively has been emphasized[4]. Preoperatively (Fig. 5), large, dilated splenic and portal veins were present, indicative of portal hypertension. Three months after a portocaval anastomosis, the procedure was repeated, indicating that the shunt was patent with adequate filling of the inferior vena cava. The caliber of the splenic vein had decreased, suggesting improvement in the degree of portal hypertension.

UNDESIRABLE COMPLICATIONS OF SPLENOPORTOGRAPHY. The procedure was done without serious complications in all patients. Untoward effects were limited to generalized warmth of the body, nausea and headaches. Such complications have been noted previously with the percutaneous injection of Diodrast via the splenic route[3,4]. Six patients had left upper quadrant pain for short intervals at the conclusion of the procedure. Ten patients studied underwent operation shortly after venography. One of this group had about 150 ml. of blood in the peritoneal cavity which we believe came from

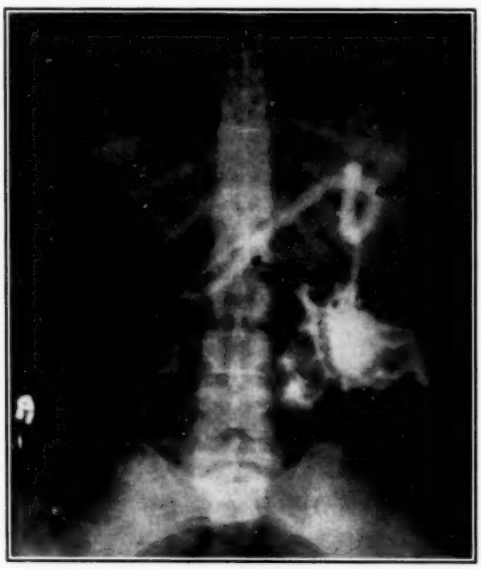

Fig. 4.—Extrahepatic Portal Obstruction.* Female, aged 34. A patient with splenomegaly and normal liver function tests. Esophagoscopy revealed large esophageal varices. Stool examinations and rectal biopsies for *Schistosoma mansoni* were negative. Splenoportogram shows a moderately dilated first portion of the splenic vein. The distal portion of the splenic vein and the portal vein are not visualized. A large collateral vein (c.v.) arises from the splenic vein and crosses the abdomen to subdivide in numerous collateral branches. The study indicates portal vein thrombosis.

*This case has been previously reported in the medical literature[5].

the splenic puncture site. However, this bleeding site had been sealed off before the operation was begun. One patient was examined at necropsy after succumbing from progressive hepatic coma. In this instance there was no evidence of bleeding at the injection site.

equipment of a general hospital. Only one anterior-posterior film need be obtained, the information regarding the splenic and portal veins being generally adequate. The projection of the radiopaque material in one plane does not allow complete interpretation for the localization of some collateral veins

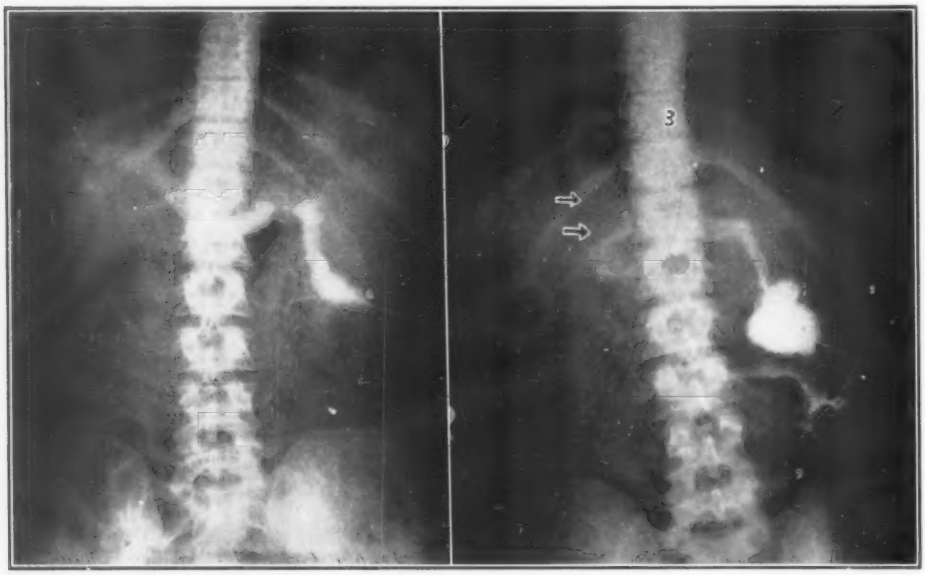

Fig. 5.—Patency of Portocaval Shunt. Male, aged 27. Splenomegaly with esophageal varices. *Schistosoma mansoni* ova found in stools and rectal biopsy. Liver biopsy indicated schistosomiasis of the liver with moderate bilharzial cirrhosis. *Left*, before portocaval shunt, tortuous dilated splenic and portal veins. *Right*, 3 months after shunt, the inferior vena cava (arrows) fills promptly establishing the patency of the shunt. The splenic vein shows a decreased caliber indicating beneficial reduction of portal pressure.

Summary. 1. Twenty-six patients had 28 successful splenoportographies in 35 procedures. The results have indicated that this technique has been well tolerated without serious complications. These studies have clarified the diagnosis of portal hypertension and allowed us to exclude extrahepatic obstruction when the patient was considered for a shunt operation.

2. The procedure can be done with the usual diagnostic roentgenographic of the portal system. However, the presence of collateral veins offers strong radiologic support for portal hypertension.

3. Splenic venography is of great clinical value in the study of portal hypertension. In patients with *Schistosoma mansoni* infection in whom liver damage is minimal, the procedure is recommended to clarify the indication for shunt anastomosis.

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SUMMARIO IN INTERLINGUA

Splenoportographia: Un Adjuncto de Valor in le Studio de Hyptertension Portal

1. Trenta-cinque splenoportographias esseva interprendite in 30 patientes. Vinti-octo del interprisas esseva completate a bon successo. Illos involveva 26 patientes. Le resultatos indica que le technica esseva ben tolerate. Il habeva nulle serie complicationes. Le studio splenoportographic ha clarificate pro nos le diagnose de hypertension portal, permittente a nos excluder obstruction extra-hepatic quando le patiente esseva considerate como candidato pro shunting chirurgic.

2. Le technica splenoportographic require nulle apparatura in excesso del usual equippamento roentgenographic que es disponibile in hospitales general. Un sol pellicula antero-posterior es requirite. Le informationes assi obtenite relative al venas splenic e portal es generalmente adequate. Le projection del substantia radio-opac in un sol plano non permitte un complete interpretation in re le localisation de certe venas collateral del systema portal. Tamen, le presentia de venas collateral offere un forte supporto radiologic pro le diagnose de hypertension portal.

3. Venographia splenic es de grande valor clinic in le studio de hypertension portal. In patientes con infection per *Schistosoma mansoni*, in qui le lesion hepatic es minimal, le technica es recommendate como medio de clarificar le question de si o non le effectuation chirurgic de anastomoses per shunting es indicate.

QUANTITATION OF THE ACTIVITY OF RHEUMATOID ARTHRITIS. 2. RECESSION OF MORNING STIFFNESS AS PATIENTS GO INTO REMISSION

By John Lansbury, M.D.
PROFESSOR OF CLINICAL MEDICINE

(From the Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania)

This paper considers "duration of morning stiffness" as it relates to the over-all activity of rheumatoid arthritis. The information presented is part of an inquiry into the feasibility of measuring the systemic manifestations of the disease which we hope ultimately to incorporate into a single system for quantitating the total activity of the rheumatoid process. The data presented below were collected from a review of office and clinic records extending over a period of 10 years.

Morning stiffness is an exceedingly common manifestation of active rheumatoid arthritis at all ages. A review of 100 consecutive cases from our files shows that it was present in 97% of these at the time of the initial interview. As we have previously pointed out[1], morning stiffness can be quantitated by observing its *duration* rather than its intensity. We found that most patients can readily distinguish stiffness from pain and that they can generally identify its duration after rising in the morning with accuracy. As the duration decreases to less than one hour, periods of duration of 5, 10, 15 or 30 minutes can be identified by the patient with even greater accuracy.

From the records of 45 unselected cases personally observed by us, we find the average duration of morning stiffness at the time of the first office visit to be 3.5 hours. In the arthritis clinic, with multiple observers, the average duration was slightly less. A rough correlation between duration of morning stiffness and activity of the disease, as measured by sedimentation rate, is apparent. Thus, in 19 cases in which the average 5-minute maximum fall of erythrocytes was greater than the median value of 5.6 mm., the average duration of morning stiffness was 4 hours, whereas in a group of 22 cases whose sedimentation rate was below the median value, the average duration of morning stiffness was 3.2 hours.

Morning stiffness tended to be more protracted in older patients. Thus, in a group of 60 patients the average duration of morning stiffness was 3.45 hours in those older than the median 51.6 years, and 2.95 hours in those younger than the median 51.6 years. However, this difference between the two age groups also held true for the sedimentation rate which averaged 6.3 mm. and 5.2 mm., respectively, for the older and younger age groups. This seems best explained on the basis of a fortuitous increase in rheumatoid activity in the older age group. The ratio between hours of morning stiffness and sedimentation rate was 0.5 for each group which suggests that both are reliable indices of rheumatoid activity.

To test further the validity of duration of morning stiffness as a quantitative index of rheumatoid activity we have analyzed serial observations of

morning stiffness from our records of 6 cases of rheumatoid arthritis who attained a *complete* remission. A remission was judged as "complete" when there was no pain at rest or on motion, no stiffness, no fatigue, no articular manifestations of inflammation and when the sedimentation rate had returned to normal and the patient could undertake full physical and occupational activity. The small number of such cases (6) available for this study is due in part to the rigorous criteria used in determining a full clinical remission and in part to insufficient serial data on hours of morning stiffness in numerous other cases which attained a full remission.

All 6 cases were treated by the standard "basic program" of rest, sedation, salicylates, blood transfusions, vitamins and physical therapy to which chrysotherapy in the form of Sodium-aurothio-sulfate (Merck) was added in an average dose of 25 to 50 mg. per week. None of the patients received ACTH or steroids, since these would have suppressed the very symptoms which we were trying to measure.

The results of this study are presented in Figs. 1, 2, and 3. In Fig. 1 the crude data of "hours of morning stiffness" are plotted against "days after treatment." It will be seen that the duration of morning stiffness drops off rapidly at first and slowly thereafter as a remission is approached. In order to ascertain whether the recession of morning stiffness occurred in a regular manner, both for the individual cases and for the group, the data were treated as follows: The in-

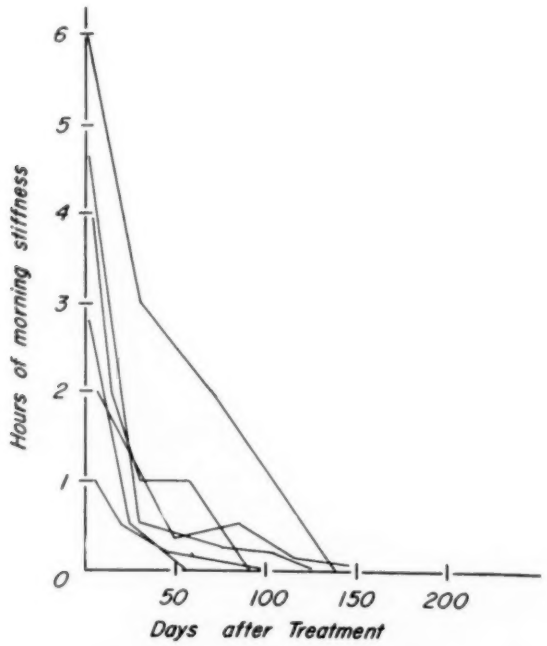

Fig. 1.—Six representative cases of active rheumatoid arthritis showing decline in hours of morning stiffness as a full remission is attained on "Basic Program" plus gold salts only.

dividual hours of morning stiffness were all brought to 100% and subsequent observations were calculated as percentage decrements from this point. The average number of "days after treatment" was likewise regarded as 100% and subsequent time intervals were calculated as percentage of average time required to attain a remission. The resulting curve seen in Fig. 2 indicates a perfectly regular parabolic trend. In viewing Fig. 2 we must emphasize that we are seeing only *the trend* of recession of morning stiffness and that this is abstracted from Fig. 1 in which the individual variations common to biological observations are manifest.

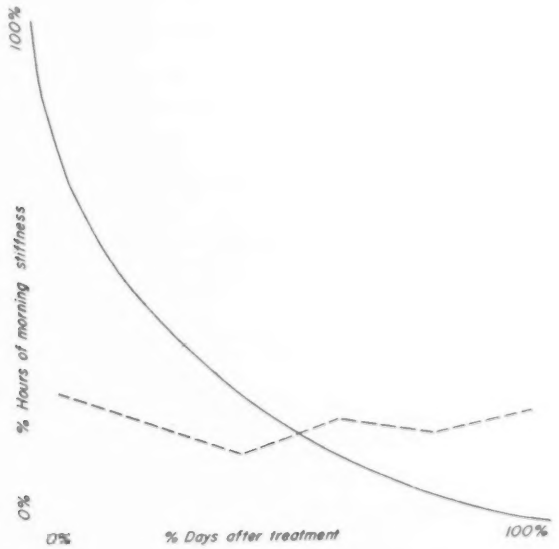

Fig. 2.—Average hours of morning stiffness in 6 cases of rheumatoid arthritis going into a clinical remission on "Basic Program" plus gold salts only.

Abscissae show percentage decrements starting as 100% for each case. Average 4.8 to 0 hours.

Ordinates show percentage of average time needed to attain a complete remission (172 days = 100%).

– – – Controls: 7 cases of active rheumatoid arthritis showing no improvement. Average hours of morning stiffness 1.4, observed for 180 days.

The regularity of the above trend was checked by standard biostatistical methods. Here, the index "hours of morning stiffness" was plotted on semilog paper for each case as "changes from 100% at the start of treatment" against "days after treatment." Fig. 3 shows this average trend, reconstituted on ordinary graph paper, and represents the average decline of hours of morning stiffness, as it actually occurred in time, for a group of 5 cases of active rheumatoid arthritis going into a full remission. The individual trends differed in no way from the average trend. The curves of trend of recession in Figs. 2 and 3 differ slightly from each other; but they confirm each other in that they indicate different aspects of the same thing, namely, *regularity* in the trend of decline of morning stiffness as patients go into remission.

In Fig. 2 the broken line represents

an average of "hours of morning stiffness" in 7 cases of active rheumatoid arthritis observed monthly for 6 months. These cases were selected from our records because our best clinical judgment indicated that their course was stationary. It will be observed that the general trend is in the direction of a straight line and thus contrasts strikingly with the trend observed for the 6 cases going into a remission. This would seem again to confirm the value of "hours of morning stiffness" as an index to rheumatoid activity.

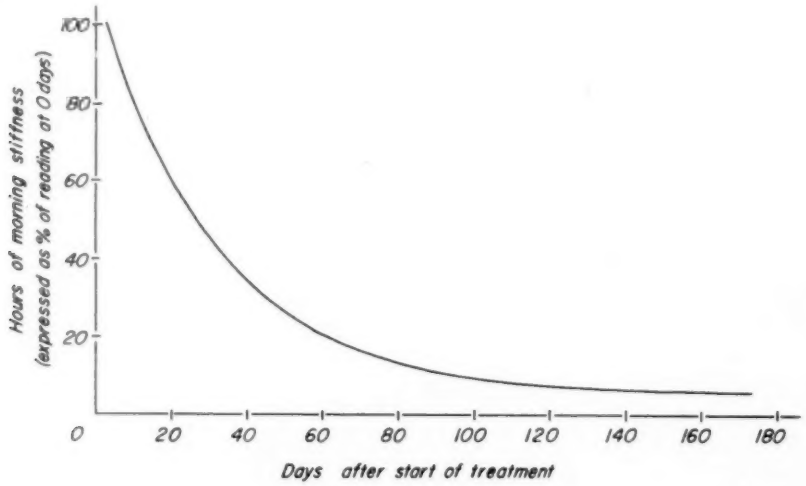

Fig. 3.—Trend of hours of morning stiffness in 5 cases of active rheumatoid arthritis going into remission. Treated with "Basic Program" and gold salts only.

Reviewing the above data, we believe that duration of morning stiffness is a valid index to the total amount of systemic or fibrositic activity of rheumatoid arthritis in the cases studied. Its place in a scheme for the evaluation of over-all activity of rheumatoid arthritis will be dealt with in a subsequent article.

Summary and Conclusions. 1) Morning stiffness is an almost universal manifestation of active rheumatoid arthritis.

2) Most patients can accurately observe the duration of morning stiffness.

3) Duration of morning stiffness correlates roughly with the maximum 5-minute fall of erythrocytes in the Cutler sedimentation rate, but appears to be unrelated to age, sex, duration of disease and hemoglobin concentration.

4) Three graphic analyses are given, which indicate that hours of morning stiffness decline in a regular trend as the patient goes into a remission.

5) Duration of morning stiffness is, therefore, a valid index to the general or fibrositic component of rheumatoid activity and so deserves to be routinely recorded as an item in progress notes.

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(Interlingua on page 66)

QUANTITATION OF THE ACTIVITY OF RHEUMATOID ARTHRITIS. 3. THE MAXIMUM 5-MINUTE CUTLER SEDIMENTATION RATE AS AN INDEX

By John Lansbury, M.D.
PROFESSOR OF CLINICAL MEDICINE

(From the Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania)

For many years the sedimentation rate has been accepted as a rough guide to the degree of systemic activity in cases of rheumatoid arthritis. Various methods for performing the test are in vogue, such as the Cutler, Westergren, Wintrobe and Rourke-Ernstene techniques, but unfortunately the results reported by these various methods cannot be compared with each other since their values, both for normal and for the abnormal, differ from each other. Our experience has been entirely with the Cutler method but we do not, therefore, imply that the Cutler method is superior to other methods. One of its disadvantages is that it is time-consuming because a technician has to make a reading every 5 minutes.

The Cutler method differs from other methods in that a wide-bore tube is employed. The completed Cutler graph has the advantage of furnishing two pieces of information: 1) the total fall of erythrocytes at the end of one hour, and 2) a series of 5-minute decrements which produce a curve from the starting point at zero to the 60-minute end-point. The shape of this curve gives information which is not apparent in the 60-minute end-point alone.

The degree of steepness of the curve can be recorded by observing the maximum fall in any 5-minute period. We have for many years routinely used this 5-minute index as a measure of activity of rheumatoid arthritis, and, with certain exceptions, have found it to be a useful measure of the severity of the disease. In stable cases, where no obvious trend for better or worse is clinically apparent, serial Cutler sedimentation curves often do not vary more than a few millimeters from each other at any point in their course over a period of many months and even years. This replication indicates a high degree of reliability for the Cutler method. Only rarely have we seen a proven case of active rheumatoid arthritis in which the Cutler sedimentation rate was not increased. However, we have observed a number of cases in which a rapid sedimentation rate, seemingly out of proportion to the mild clinical manifestations, persisted. But, in the great majority of cases we have the impression that the rate of fall of erythrocytes parallels the degree of activity of the rheumatoid process. Especially in those cases going into a remission have we found that the sedimentation curves serially straighten out toward an almost horizontal diagonal line, with only occasional deviations from a steady trend toward normality. On the other hand, a single recording of the fall of erythrocytes at the end of one hour (sometimes referred to as the Cutler Index) seems to be a much less sensitive index, since often an impressive decrease in it is noted only after the patient is well

on his way to remission. We have, therefore, relied on the maximum 5-minute fall as an index of activity.

With this information in hand, it seemed worth-while to see if the 5-minute Cutler index was quantitatively related to the over-all activity of rheumatoid arthritis. The following data were obtained from a review of our private and clinic records.

In order more thoroughly to test the validity of the maximum 5-minute sedimentation rate as an indicator of rheumatoid activity, it is necessary to observe the decline of this index in a series of patients going into a full remission. If the decline occurs in a regular manner, it may be concluded that even small decreases in the maximum 5-minute fall of erythrocytes are

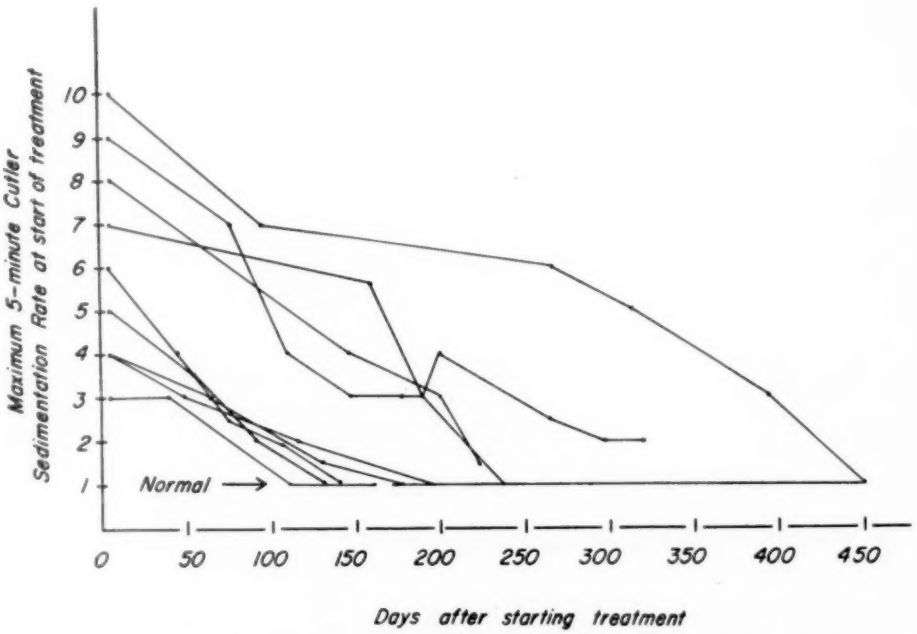

Fig. 1.—Crude data on 5-minute Cutler ESR in 10 cases of active rheumatoid arthritis going into a remission under treatment with standard "Basic Program" plus gold salt therapy.

In 100 consecutive cases of rheumatoid arthritis the average maximum 5-minute ESR at the time of the initial observation of the patient was 5.6 mm. The older age group had a slightly increased average fall (6.3 mm.) and the younger age group a lesser fall (5.2 mm.), this small difference is of questionable significance. In our cases no definite relationship between the sedimentation rate and sex, anemia or duration of disease was found.

significant. The data presented here were abstracted from the charts of patients who attained a full clinical remission as previously defined[1]. All were treated by the basic program plus gold salts, none by steroids.

Figure 1 depicts the crude data from 10 cases of rheumatoid arthritis going into full clinical remission. The normal maximum 5-minute sedimentation index is 1 mm. or less. This was attained in all but 2 cases which otherwise ap-

peared to be in a full remission. The time required to attain a remission varied from 100 to 450 days. It will be seen that, in general, the higher the sedimentation rate, the longer it takes to attain a remission. Only 3 of the 10 curves show striking deviations from the general downward trend to normality. Such deviations are to be expected in any biological data and curves, when averaged and plotted, produced a very shallow "S" shaped curve which, for practical purposes, can be considered as a diagonal line. The broken line represents the average maximum 5-minute sedimentation rate in 6 cases whose course appeared to be clinically stationary. The observations were made at monthly intervals. It will be noted that the general trend is in

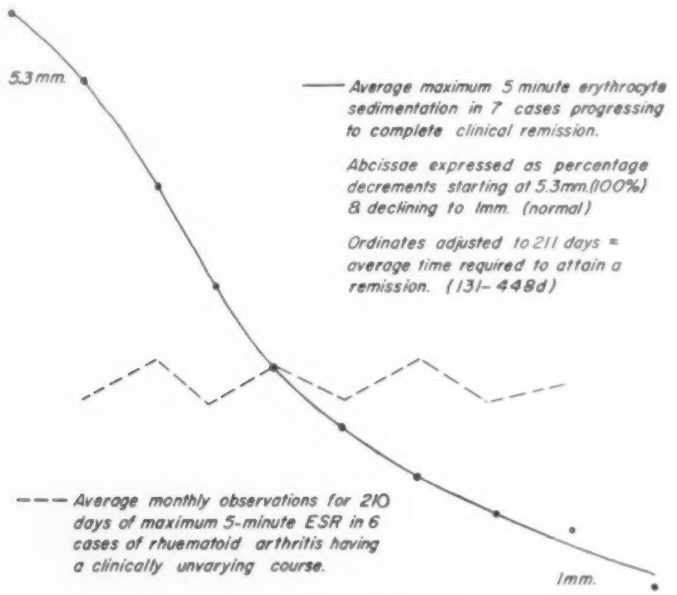
5.3mm.
Average maximum 5 minute erythrocyte sedimentation in 7 cases progressing to complete clinical remission.
Abcissae expressed as percentage decrements starting at 5.3mm.(100%) & declining to 1mm. (normal)
Ordinates adjusted to 211 days = average time required to attain a remission. (131–448d)
Average monthly observations for 210 days of maximum 5-minute ESR in 6 cases of rheumatoid arthritis having a clinically unvarying course.
1mm.

Fig. 2.—Five-minute maximum sedimentation (Cutler) in 13 cases of rheumatoid arthritis treated with "Basic Program" plus gold salts (no steroids).

do not significantly alter the general trend for the group.

Figure 2 shows the average decline in maximum 5-minute ESR in 7 cases under our personal observation. The average was obtained by giving each initial ESR reading the value of 100% and expressing changes from this as percentage decrements from 100. The average time required to attain a remission was 211 days. This was likewise taken as 100% for each case and ordinates were adjusted to percentages of 211 days. The resulting individual a horizontal line, which contrasts strikingly with the downward trend of the cases going into remission.

Figure 3 portrays an analysis by standard biostatistical methods of the same data. The shallow parabolic curve results from graphing the crude data on semi-log paper and reconstituting the average so obtained on ordinary graph paper. By this method some individual lines showed significant deviations from the general trend, so that it is a question whether the general trend is better defined by a

diagonal line or by a shallow curve. In either event, both methods indicate a *regular* trend for the group as a whole, and we may therefore conclude that, subject to the expected individual biological variations, the 5-minute ESR by the Cutler method is a valid indicator of the total inflammatory response of the body to rheumatoid arthritis. Its place in an over-all scheme of evaluation of rheumatoid activity will become clear as other indices become available for comparison. It is hoped that deviations from the general trend in this and other indices will cancel each other when they are summed up in a total index.

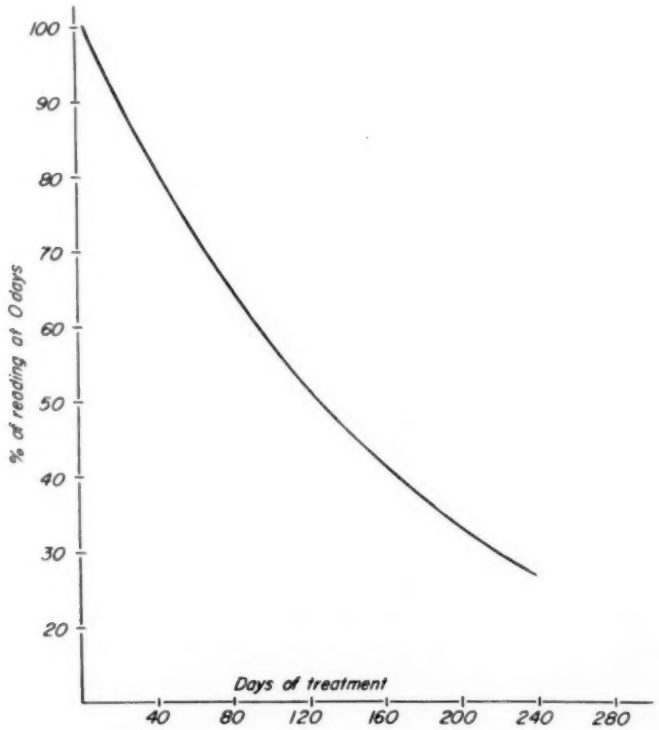

Fig. 3.—Trend of 5-minute Cutler sedimentation rate in 10 cases of active rheumatoid arthritis going into remission under treatment with "Basic Program" plus gold-salt therapy (no ACTH or steroids).

It is possible that other methods, particularly the Rourke-Ernstene and Westergren methods may provide equally reliable or even superior indices. We hope that rheumatologists who use these other methods will undertake a similar analysis from their records of cases going into remission. It is important to note that such studies must be done on patients *not* receiving ACTH or steroid therapy, since these agents suppress the ESR and other indices which we are trying to measure.

Summary and Conclusions. 1) The maximum 5-minute fall of erythrocytes observed by the Cutler sedimentation

technique averaged 5.6 mm. in a series of 100 consecutive cases of rheumatoid arthritis at the time of their first interview.

2) A statistical analysis of the 5-minute ESR in 10 cases of rheumatoid arthritis going into remission indicates a trend toward normal, both for individuals and for the group, which is sufficiently regular to validate the Cutler 5-minute ESR as a quantitative index of systemic rheumatoid activity.

3) Other sedimentation methods, such as the Rourke-Ernstene and Westergren deserve to be similarly evaluated.

ACKNOWLEDGMENT: We wish to thank Dr. Spencer M. Free, Jr., for valuable assistance in the biostatistical evaluation.

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SUMMARIO IN INTERLINGUA

Quantitation del Activitate de Arthritis Rheumatoide 3. Maximo de Sedimentation per 5 Minutas (Secundo Cutler) Como Indice de Activitate

1. Le maximos de sedimentation erythrocytic per 5 minutas, observate per medio del technica sedimentational de Cutler, monstrava un valor median de 5,6 mm in un serie de 100 consecutive casos de arthritis rheumatoide al tempore del prime interview.

2. Le analyse statistic del valores de sedimentation erythrocytic pro periodos de 5 minutas a base de 10 casos de arthritis rheumatoide in progresso verso remission exhibi un tendentia de normalisation, tanto in individuos como etiam in le gruppo. Iste tendentia es sufficientemente regular pro validar le technica Cutler del determination de sedimentation erythrocytic pro periodos de 5 minutas como indice quantitative del activitate rheumatoide systemic.

3. Altere technicas de mesuramento sedimentational (per exemplo le technica de Rourke-Ernstene e de Westergren) merita un simile evalutation.

THE LACK OF EFFECT OF INGESTED FERROUS SULFATE ON THE GUAIAC TEST FOR OCCULT BLOOD IN THE STOOL

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The administration of iron in one form or another by the oral route is usually employed to treat the anemia resulting from bleeding lesions of the gastrointestinal tract. Ingested iron not absorbed in the intestine is excreted in the stool as iron sulfide which colors the stool greenish black, or black[2]. This color is easily confused with that black color produced by changed blood in the stools. Consequently gastrointestinal bleeding in the patient receiving iron salts orally cannot be detected by inspection of the stool, and a specific test for occult blood must be used.

Varying opinions are expressed by clinicians regarding the validity of tests for occult blood in the stool of the patient taking iron orally. Indeed, clinical investigation has also yielded conflicting results. Johnson and Oliver[3] reported that in seven individuals on a meat-free diet who were given 0.3 gm. ferrous sulfate three times daily for 4 days, the stools were not only tarry in color but gave a very prompt positive reaction with guaiac. At no time before nor after these patients were given iron salts were tarry colored stools or positive tests for occult blood found. Burger[2], on the other hand, reported that two subjects on a meat-free diet who were given 1 gm. iron ammonium citrate a day passed tarry black stool within 24 hours, but that the stools did not give a positive reaction when tested for occult blood with powdered gum guaiac.

The production of color in the guaiac test for occult blood depends on the oxidation of phenolic compounds to quinones which yield colored products by intermolecular reaction. Such oxidation can be brought about by hydrogen perioxide, and this reaction can be catalyzed by many substances, some of the most effective of which are peroxidases. Naturally occurring peroxidases contain a hemin-like moiety. Hemoglobin exhibits peroxidase-like activity and facilitates the oxidation of phenolic compounds by hydrogen peroxide. Gum guaiac contains an oxidizable phenol designated *guaiaretic acid* which on oxidization yields a compound of unknown composition, deep blue in color[1]. It is known that iron does not catalyze this reaction and hence gum guaiac in the presence of iron would not be expected to yield a blue color.

To determine whether ingested iron does give a false positive test for occult blood, observations were made on specimens of stool of 116 individuals given ferrous sulfate orally. The present communication reports these observations.

Materials and Methods. In the last two successive years members of the second year class of the Johns Hopkins Medical School, as part of the work in laboratory diagnosis, have taken ferrous sulfate* 0.3 gm. three times daily for 3 days before the laboratory session in which they collected and examined their own stools. All the students ate their usual diet except that all were requested to eat meat well cooked in addition to taking the ferrous sul-

*Kindly furnished by Mr. Robert Smith of the Upjohn Company.

fate. Tests to determine occult blood were performed by each individual on his own stool using the guaiac method outlined below. In addition each student performed as controls the test on specimens of several stools collected from other patients and subjects. The single stool specimens examined by all students were: A) a normal stool, B) stools obtained from 2 patients recuperating from myocardial infarctions who had been given ferrous sulfate orally 0.3 gm., three times daily for one week, C) stool obtained from a patient who had a bleeding duodenal ulcer and had been passing tarry stools for a week or longer, and D) stool furnished by a member of the class who had been on a high rare meat diet (1½ pounds rare steak a day) for 3 days before the stool specimen was obtained.

TESTING FOR OCCULT BLOOD IN STOOL WITH GUM GUAIAC. 1) A small amount of stool is placed upon a piece of filter paper and two drops of glacial acetic acid are added to the stool. 2) Two drops of a freshly prepared solution of ethyl alcohol saturated with powdered gum guaiac are added to the stool. 3) Two drops of 3% aqueous hydrogen peroxide are added to the stool. 4) The reagents are mixed thoroughly with the stool by stirring with an applicator stick, and the color reaction on the filter paper is observed immediately and in 5 minutes. 5) Simultaneously a blank is run to determine the background color reaction, if any, of the reagents and filter paper, and also a test is run on a drop of venous blood to determine the color of a known positive reaction. 6) An immediate developing deep blue color is interpreted as a positive reaction indicating the presence of blood, a faint blue color developing within 5 minutes is interpreted as a weakly positive reaction, yet still indicating the presence of blood, but presumably a small amount. The development of a greenish color is interpreted as a negative reaction.

Results. Table 1 shows the results of the observations made by the students. There was only one positive reaction using the blank, and no negative reactions when blood was used. Prior testing of the normal stool by the instructor and the clinical laboratory had established that there was no occult blood in the stool. One student obtained a positive reaction on this stool. The patient with the bleeding ulcer was purposefully not on iron therapy. One hundred and fourteen students detected blood in the stool of a patient with a bleeding ulcer, whereas two did not. When each student studied the stool of a patient on the ward fed iron salts, 4 reported a positive reaction. Numerous specimens of stools from these patients examined before and

TABLE 1. STUDENT OBSERVATIONS

Material Tested	*Total Number Determinations*	*Reaction to Gum Guaiac*	
		Positive	*Negative*
Blank	116	1	115
Venous Blood	116	116	0
Stool A.—Single specimen normal stool previously tested by instructor, found to have a negative reaction.	116	1	115
Stool B.—Three specimens black tarry stool, random hospital patient on iron salts orally for one week.	116	4	112
Stool C.—Single specimen formed tarry stool, patient with bleeding duodenal ulcer.	116	114	2
Stool D.—Single specimen stool of student on high rare meat diet.	116	1	115
Stool E.—Black, tarry stools of students on iron salts orally for three days.	116	6 (Three subsequently proven to have bleeding lesions.)	110

after iron salts had been given never showed a positive reaction to guaiac when tested in the clinical laboratory. When each student studied his own stool containing iron, 6 reported a positive reaction. These 6 students were examined and 3 were found to have hemorrhoids which could have been bleeding. Stools examined subsequently (2 weeks after ingestion of iron salts) gave a positive reaction in 2 students.

Discussion. There was one positive reaction reported among the 116 examinations made on a normal stool presumably free from blood, and one positive reaction reported among the 116 examinations made on the blank runs using the reagents alone. There were eight positive reactions reported out of 229 examinations made on stools containing iron but presumably free from blood. These reported positive reactions in the three groups of examinations could occur from errors in interpreting the color reactions. Comparison of the figures does not indicate any difference in the two groups and one presumes, then, that the positive reactions reported are due to chance error in methodology or interpretation and do not indicate a positive reaction to iron salts. The single positive reaction in the stool of the subject on a high rare meat diet may well be due to chance error in methodology or interpretation.

Summary. The reliability of the test for occult blood in the stools using gum guaiac was established by:

1) Well controlled observations made upon the stools of normal patients, a patient with a bleeding ulcer and 116 students and 2 patients who took iron orally, and upon the stool of a subject on a diet high in rare meat.

2) Ferrous sulfate ingested orally, though giving a black or tarry color to the stools, does not give a positive reaction with the gum guaiac test for occult blood.

3) The amount of blood contained in the stools of a patient who ingests an average portion of rare meat does not give a positive reaction to gum guaiac.

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SUMMARIO IN INTERLINGUA

Le Non-Effecto del Ingestion de Sulfato Ferrose Super le Test a Guaiaco pro Sanguine Occulte in le Feces

Le autenticitate del test a guaiaco pro sanguine occulte in le feces esseva establite per medio de ben controlate observationes del feces de patientes normal, de un patiente con un ulcere sanguinante, de 116 studentes e 2 patientes qui recipeva ferro per via oral, e de un subjecto qui se manteneva super un dieta ric in carne crude.

Le ingestion oral de sulfato ferrose resulta in feces de color nigre o catranose sed non produce un reaction positive in le test a guaiaco pro sanguine occulte.

Le quantitate de sanguine continite in le feces de un patiente qui ingere portiones normal de carne crude non produce reactiones positive in le test a guaiaco.

THE TREATED PULMONARY LESION AND ITS TUBERCLE BACILLUS
I. PATHOLOGY AND PATHOGENESIS

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The pathology of pulmonary tuberculosis is entering a new era. Since the advent and widespread clinical usage of the specific chemotherapeutic agents, the classical lesion has undergone significant qualitative and quantitative alterations. This study is limited to the effects of the two most important of these. It will combine observations made in this laboratory with published experimental (Feldman, Hinshaw, Mann, and Karlson[9,10,11], Steenken and Wolinsky[30] and Youmans and McCarter[35]) and clinical (Auerbach, Katz and Stemmermann[1,2,3], Baggenstoss, Feldman and Hinshaw[4], D'Esopo *et al.*[8], Flory *et al.*[12], Kidd[17], Mahon[21] and Silverthorne and Silverman[29]) results following the use of streptomycin and the experimental (Grunberg *et al.*[13], Karlson and Feldman[15], and Steenken and Wolinsky[31]) and clinical results (De Figueiredo and de Paola[6], Denst[7], Johnson and Hewitt[14], Katz and Klopstock[16], Medlar[22], and Thompson[33]) after isoniazid therapy. Most of the changes are a matter of record and will be only briefly outlined. The following discussion will be concerned more with pathogenesis, because it is believed that the altered morphology can be explained readily on the basis of a modified pathogen (the tubercle bacillus) calling forth a modified inflammatory reaction which results in a modified repair process.

Materials and Methods. The principal material used in this study consisted of 69 surgical specimens received in the period between March, 1954, and November, 1955. They were the results of 11 pneumonectomies, 1 bilobectomy, 24 lobectomies, 28 segmental resections and also included 5 specimens that consisted of a lobectomy plus a wedge or segmental resection. A special routine was devised for the examination of the tissue. From the operating room it was taken directly to the bacteriology laboratory where it was dissected in the fresh state under sterile conditions. The gross characteristics and geographic location of the lesions were recorded. All cavities were classified as open or closed. Special note was made of the contents, the character of the lining and the thickness of the wall. Material within the bronchi and all intrapulmonary pathologic processes were sampled for bacteriological study. The precise methods used will be outlined in the following paper. The specimen was then placed in a 10% solution of formalin and removed to the pathology laboratory. Following complete fixation, it was re-examined carefully and the gross findings were compared with the observations made previously. Appropriate blocks were taken for microscopic examination. Hematoxylin and eosin and acid-fast stains were made routinely and special stains were done where indicated.

Pathology. The more important pathological changes are briefly summarized in the following paragraphs. Because it is believed that the resulting morphologic alterations produced by the administration of streptomycin and isoniazid are significantly different, they will be listed under individual headings. In most of the above studies, para-aminosalicylic acid was given in conjunction with both of these drugs. The nature of this compound and the magnitude of its action suggest that it has no significant role in the tissue response. Therefore, it will not be considered in the following discussion.

CHANGES ASCRIBED TO STREPTOMYCIN. The following morphologic modifications of the classical tuberculous lesion have been found to occur after the administration of streptomycin.

1. The classical picture of miliary tuberculosis was strikingly tempered. The amply treated lesion was sharply outlined and completely fibrosed. It occasionally contained a few macrophages and lymphocytes. In these instances, no specific evidence of preexisting tuberculosis was found. When caseation did remain, there was an exaggeration of the surrounding collagen. Significantly, tubercle bacilli could be demonstrated in both types of lesion.

2. There was a marked diminution of the perifocal reaction around larger tuberculous processes. The alveoli were empty, and, because of the reduction in the inflammatory exudate, the so-called "nonspecific" component of the capsule was reduced in thickness.

3. Bronchiolar disease was quantitatively decreased. Scars within the wall were rare and healing with reepithelization at the bronchocavitary junction was common.

4. A clearly demonstrable effect on the cavity walls was lacking. In the great majority of instances, they showed well developed wide interzones of necrosis surrounded by epithelioid cells and granulation tissue. There was an insignificant increase in the fibrotic reaction.

CHANGES ASCRIBED TO ISONIAZID. 1. The giant cells were atypical in structure and location. The number of nuclei varied from 6 to over 50. As is shown in Fig. 1 (*A*), these were frequently spread at random throughout the cytoplasm, suggesting a foreign body type rather than the classical Langhans' variety. The pattern of cell distribution was markedly different from that commonly encountered in pulmonary tuberculosis. These unusual cells were often distantly removed from the acute processes of caseation and tubercle formation. They were free in alveoli, in intrabronchial mucous plugs (Fig. 1 *[B]*), surrounded by large numbers of lymphocytes or found deeply buried in bundles of collagenous tissue (Fig. 2). In the material used for this study, these cells appeared to be mature on microscopic examination.

3. Random collections of xanthoma cells were seen in increased numbers. Along with the lipid inclusions in giant cells, they reacted positively to fat stains. Perhaps related to this phenomenon was the occurrence of asteroid, spiculated and calcified Schaumann bodies. Heretofore, these have been an extremely rare finding in pulmonary tuberculosis.

4. Granulomatous reactions suggestive of the lesion described in Boeck's sarcoid were noted. These had the appearance of a self-limited, fibrosing, rounded expansion of epithelioid cells. Their centers sometimes contained a noncaseous, granular, central necrosis with a lymphocytic infiltration. An example is shown in Fig. 3.

5. Atypical proliferation of smooth muscle around bronchioles was not uncommon. Figure 4 illustrates such an

overgrowth into an otherwise uninvolved area.

6. The formation of collagen was exuberant. This was even more marked than that seen in those patients receiving streptomycin. The resulting bundles were not only increased in number but also in thickness. A partial explanation was found in the larger quantities of healthier appearing granulation tissue.

7. By far the most remarkable change occurred in approximately 19% of the cavities studied in this laboratory and approximately 10% of the cavities described in the recent literature (Katz and Klopstock[16] and Thompson[33]). As end-stage products they had smooth, glistening, and sometimes trabeculated linings. Their walls were fibrous, markedly thinned, hemorrhagic, and hyperemic. These were sharply demarcated from a relatively uninvolved surrounding parenchyma. In some of the cavities the lumen contained serosanguinous fluid. Even though many of them apparently arose from bronchi, microscopic examination revealed no autochthonous epithelial lining. The

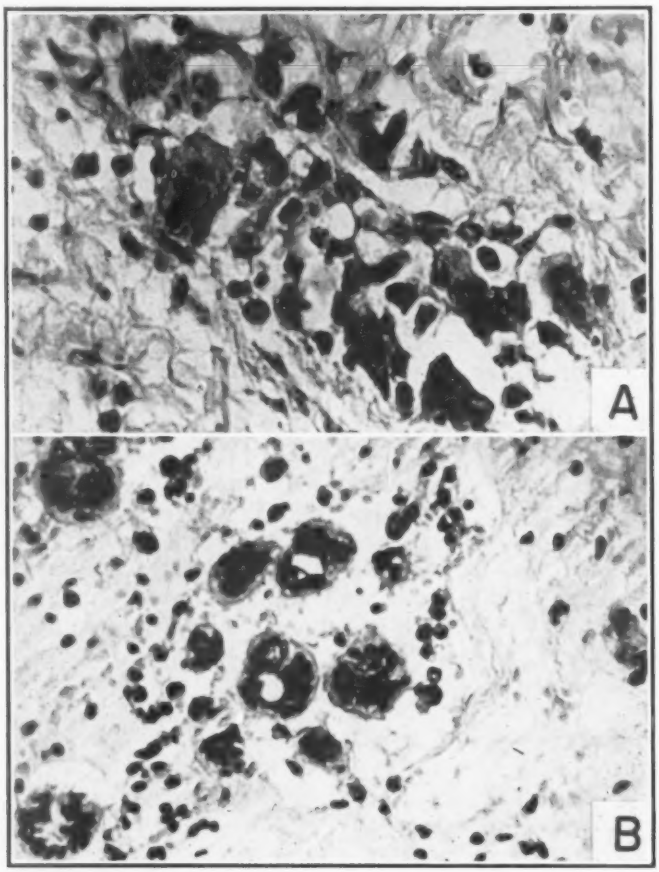

Fig. 1.—Aggregation of atypical giant cells: (*A*) surrounded by fibrous tissue, and (*B*) within an intrabronchial mucous plug. × 430

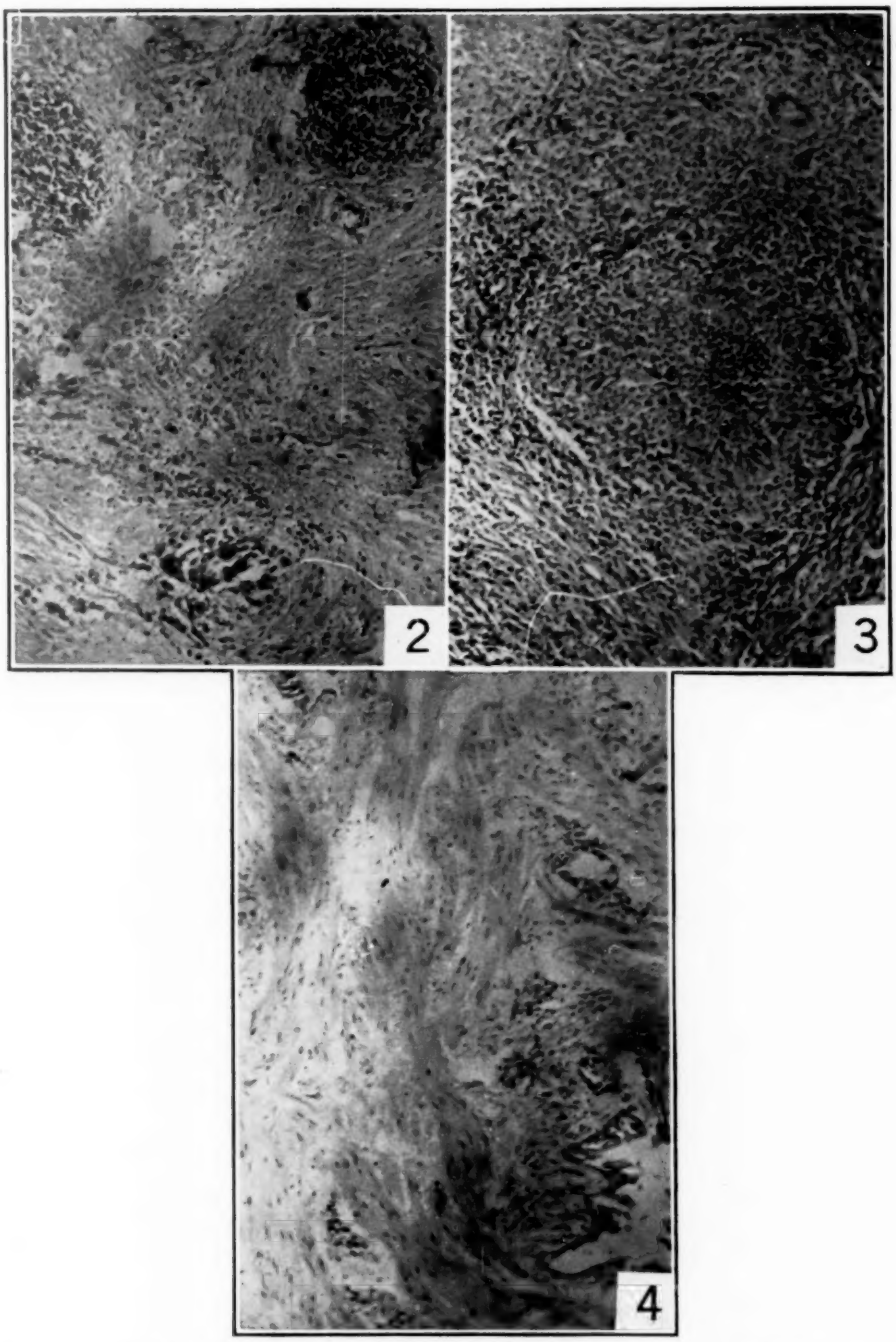

Fig. 2.—Masses of lymphocytes and a collection of giant cells buried deep in collagen. × 100

Fig. 3.—Granulomatous reaction with central granular necrosis and lymphocytic infiltration suggesting the lesion of Boeck's sarcoid. × 100

Fig. 4.—Atypical peribronchiolar proliferation of smooth muscle into an otherwise uninvolved area. × 100

fibrocytes of the wall were in direct contact with the space. This was not surprising when one realizes that the preceding destructive necrosis had eliminated the potential source of regeneration, the basal epithelial layer. In those cavities, however, in which a communication to the outside could be demonstrated, it was not uncommon to find proliferation of the adjoining bronchial epithelium with extension for short distances along the inner sur-

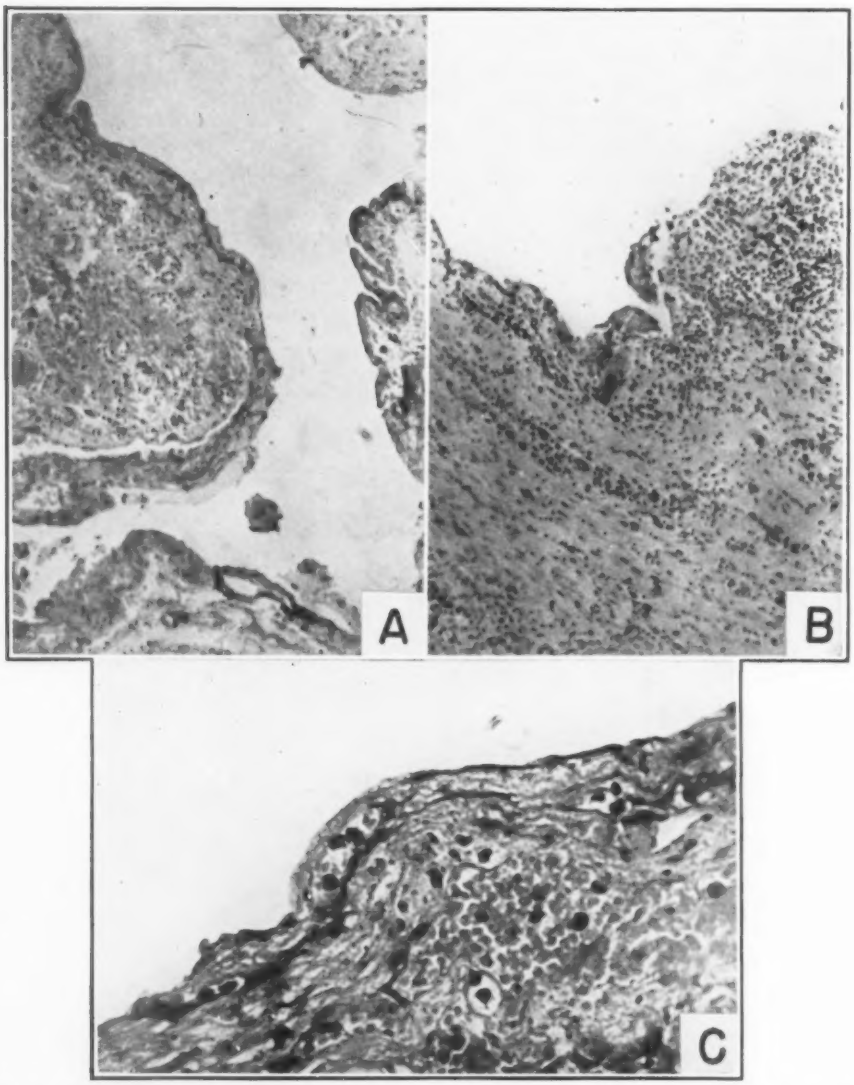

Fig. 5.—Sequential healing of end-stage cavity: (*A*) Large segments of wall still lined by caseous membrane (× 100); (*B*) Residual fragments of caseum adjacent to lympho- and mono-cytic inflammatory reaction (× 100); (*C*) Higher magnification of segment of (*A*) showing fibrinous necrosis and hyperemia. × 430

face. Grossly, they frequently had the appearance of giant air cysts, or bullae.

Transitional phases ranging from caseation to complete clearing were readily found. Examples of these are illustrated sequentially in Figs. 5, 6, and 7. They will be discussed in greater detail under Pathogenesis.

Pathogenesis. The process of inflammation and repair in mammalian tissues has a definite pattern of response. This is determined by the inciting agent. Pertinent to the present study, there

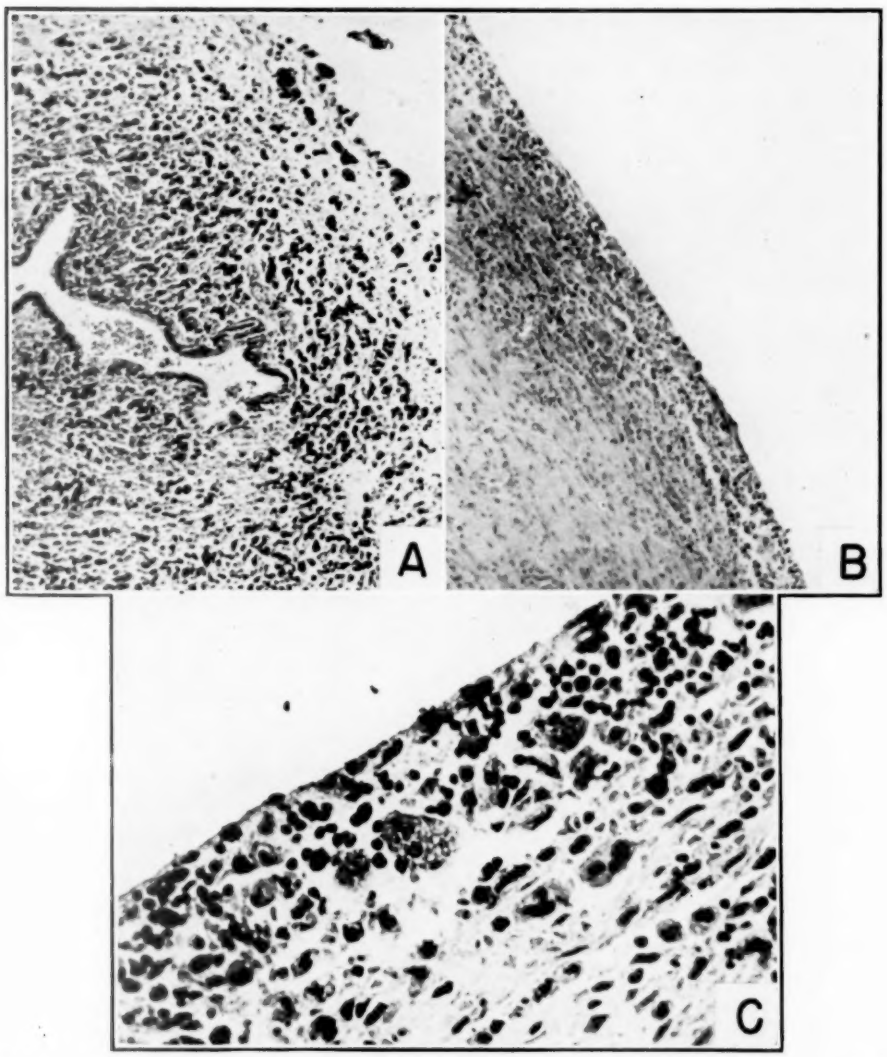

Fig. 6.—Sequential healing of end-stage cavity (continued): (*A*) Histologically uneven lining (upper right) overlying inflamed wall and a relatively normal bronchiole (× 430); (*B*) Diminished inflammatory reaction (× 100) composed of (*C*) lymphocytes, monocytes, epithelioid cells and vacuolated giant cells. × 430

have been collected a substantial number of reports that indicate a fundamental alteration of this particular inciting agent, the tubercle bacillus. Primarily responsible for this change are the various therapeutic substances given in an attempt to control the clinical course of the resulting disease process. Secondarily, but of equal importance, is the strengthening of the

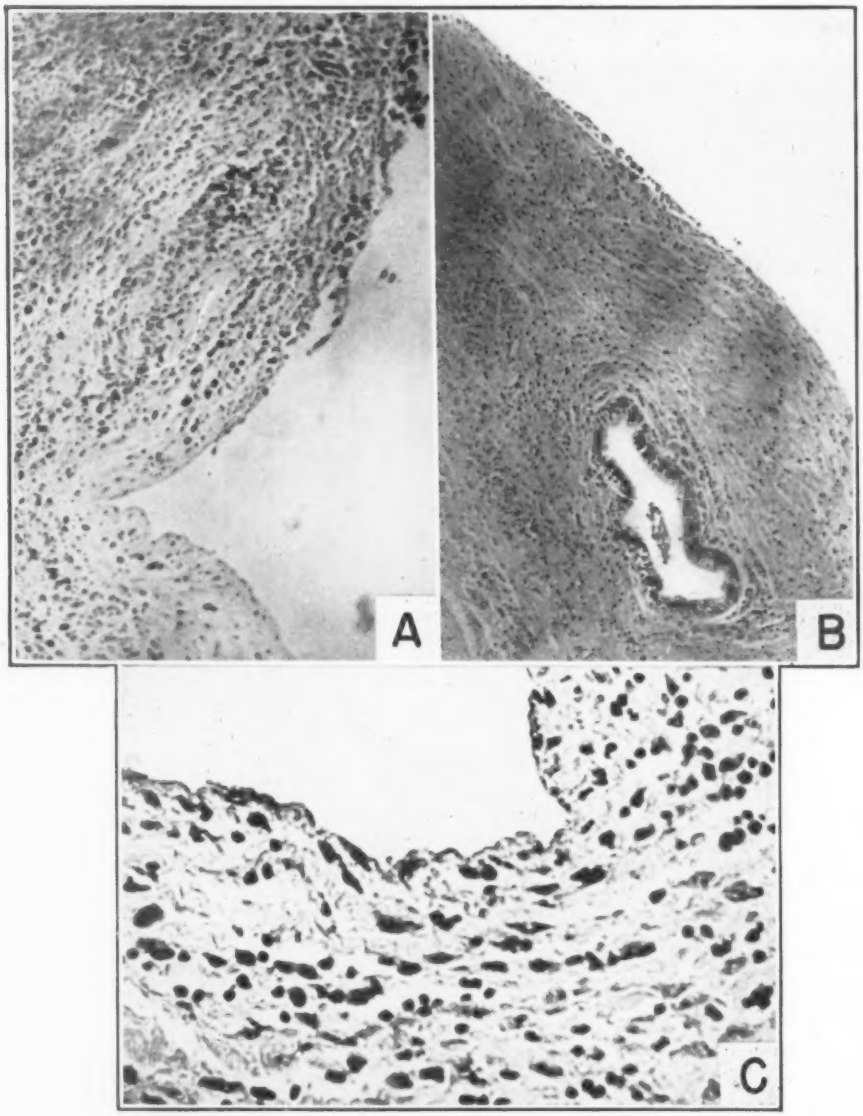

Fig. 7.—Sequential healing end-stage cavity (concluded): (*A*) Area still microscopically ragged adjacent to smooth segment showing more advanced healing (× 100); (*B*) Healing almost complete (× 100); (*C*) Higher magnification of final phase with minimal inflammatory reaction remaining. × 430

host resistance made possible by this chemotherapy.

The ultimate consequence is probably determined by two different factors: 1) the site of action of the drug with respect to the individual cell, and 2) the action of the drug on the fundamental metabolic process of the bacillus.

A number of authors have clearly shown that the site of effective action differs with the drug employed (Mackaness[19], Mackaness and Smith[20], and Suter[32]). Using living macrophages, streptomycin was found to be most strongly antibacterial when the microscopic organisms were extracellular and only weakly antibacterial when they were intracellular. Isoniazid is equally bacteriocidal against both intra- and extra-cellular bacilli. Middlebrook and Yegian[23] and Schaefer[28] believed that the bacteria are most vulnerable when they are multiplying. Barclay and his associates[5], by labeling isoniazid with radioactive carbon, found that this drug, or its metabolites, had the capacity of penetrating into both cavitary and caseous lesions. Of some interest was the drug's high concentration in the fibrous capsules of the latter. After assaying the caseous centers of tuberculomata, Mahon[21] concluded that streptomycin, on the other hand, lacked the power of effective penetration. Vishwanathan and his colleagues[34], using the electron microscope, illustrated excellently the various stages of disintegration experienced by the tubercle bacillus following *in vitro* exposure to streptomycin. The findings of Koch-Weser, Barclay and Ebert[18] strongly support the belief that streptomycin is bacteriostatic, while isoniazid is bacteriocidal. Oestreicher and his colleagues[24] recently reported findings that are pertinent to this present study. They showed that the pathogenic potentialities of isoniazid-resistant mutants of the tubercle bacillus are strictly limited.

The precise mechanism by which these compounds act is yet to be shown experimentally. From the material now available, however, it seems justifiable to assume: 1) that the over-all number of bacteria is reduced, 2) that in this reduction there is actual destruction of a large number of tubercle bacilli which probably permits free diffusion of their various chemical constituents throughout the tissue, 3) that the resulting mutants are pathogenetically different, and 4) from studies conducted in this laboratory, the metabolic process of the remaining bacteria can be rejuvenated with time and the proper cultural conditions. This has been most strikingly shown in material taken from closed cavities and tuberculomata.

Sabin and others[25,26,27] have demonstrated conclusively that the several chemical components of the tubercle bacillus can cause specific inflammatory reactions when separately injected into the experimental animal. The sum of these make up the classical pathological picture of tuberculosis.

The above results indicate that these experiments are repeated in a modified form when the disease is treated with chemotherapeutic agents. This is particularly well illustrated in those patients receiving isoniazid. A certain number of tubercle bacilli are killed by the drug. The body defenses cause destruction of the dead organisms, and the various chemical constituents are freed. Following diffusion into the surrounding tissue, each may call forth its own explicit inflammatory reaction. Specific examples illustrating this phenomenon are the atypical number, form and location of the giant cells and the unusual collections of lymphocytes in the most unanticipated sites. It is of singular note that these two inflamma-

tory elements were not infrequently found together.

The quantitative reduction of the caseous necrosis and the perifocal exudative reaction are the result of an aborted early stage during which the drug exerts a paralyzing effect on the tubercle bacillus. The complete fibrosis of the miliary lesion, the appearance of more florid granulation tissue and the exuberant overgrowth of collagen represent a more aggressive response with strengthening of the body's defensive and reparative capacity.

Of special interest is the phenomenon of cavity healing. Histologically, the pattern of repair was a logical one. The original caseum and degenerate granulation tissue appeared to be replaced by more fibrinous necrosis (Fig. 5 *[A] [C]*). With the quantitative reduction of the caseous membrane, a fresh, robust appearing inflammatory exudate infiltrated the adjacent wall (Fig. 5 *[B]*). It was composed of large numbers of lymphocytes, fewer monocytes and plasma cells and an occasional epithelioid and vacuolated giant cell (Fig. 6). Infrequently eosinophils appeared. As healing progressed, the exudation gradually cleared leaving only a compact network of healthy appearing fibrocytes (Fig. 7). This was the end-stage cavity described above.

Before the era of specific drug therapy, the mechanism just described was an extremely rare occurrence. It was still very infrequent with the administration of less effective agents, such as streptomycin. With the addition of isoniazid, present findings indicate that it is now not rare.

The majority of the patients supplying material to this study were receiving isoniazid prior to operation. A few received only streptomycin as the principal drug. In view of the experimental evidence cited above, it is not difficult to conceive of an adequate drug concentration within the cavity. The relative effectiveness of these two drugs has already been pointed out. With their ability to obstruct bacterial activity, the body defenses are more easily mobilized and the necrotic debris is cleared away. The following paper presents strong evidence to support the concept of complete sterilization of the end-stage cavity. As will be discussed in greater detail, tubercle bacilli could not be cultured even after prolonged incubation.

The findings described above have strong clinical implications. Diagnostically, they are generally appreciated and can be readily demonstated by Roentgen ray. Therapeutically, they suggest the necessity of a re-evaluation of current chemotherapeutic and surgical concepts. A more detailed discussion of this facet of the problem will be given in the following paper after the bacteriological data have been presented.

The much higher incidence of end-stage cavities in the specimens studied here can probably be explained by the relatively high ratio of cases referred for surgical resection.

Summary. The pathology of pulmonary tuberculosis is changing. These changes, based on the findings in this laboratory and the observations of others, are outlined. It is believed that the widespread use of increasingly effective chemotherapy is responsible for this phenomenon. Pathogenetically, it represents a modification of the classical response of inflammation and repair. The two most currently successful drugs, streptomycin and isoniazid, have the ability to attack the tubercle bacillus directly. By doing so, they materially aid in the prevention of multiplication, slow down metabolic processes and, in the case of the latter, permit actual destruction of the microörganism. The pathologic evidence given

here is indirect. The bacteriologic findings given in the following paper are derived from the same material and offer further valuable data. These observations indicate that, as more competent drugs are discovered and employed, the pathology of pulmonary tuberculosis will present an even more striking metamorphosis. As a consequence, a re-evaluation of the current concepts of both medicinal and surgical therapy seems to be indicated.

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(Interlingua on page 49)

THE TREATED PULMONARY LESION AND ITS TUBERCLE BACILLUS.* II. THE DEATH AND RESURRECTION

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This second paper is built around two very distinct and fundamental problems encountered in pulmonary tuberculosis and their pathobacteriologic correlation. The first concerns the possible autonomous or drug sterilization, or both, of the tuberculous lesion. This necessarily includes any changes in viability or metabolic activity of the tubercle bacillus. The second problem concerns the adaptive modification of viable bacilli by the chemotherapeutic agents.

Several workers (Beck and Yegian[2], D'Esopo *et al.*[4], Medlar[9], Medlar, Bernstein and Steward[10], and Yegian[18]) in recent years have found lesions within the human body to contain microscopically visible acid-fast bacilli that do not grow on culture media, thus, emphasizing the question of life or death of these tubercle bacilli. This observation is not new, for it was demonstrated in 1929 by Griffith[6] and later by Sweany[15]. This phenomenon therefore, did occur prior to the advent of antituberculosis drugs. It cannot be assumed then, under these conditions, that drugs are solely responsible for this nonpropagable condition of tubercle bacilli. D'Esopo and associates[4] have stated that bacilli die in certain tuberculous lesions even without the benefit of drugs. Canetti[3] has stated the ratio of microscopically visible to cultural tubercle bacilli increases as does the development of caseum. It may be true that antituberculosis drugs have increased this noncultural status of visible bacilli. It is certainly true that chemotherapy has increased the occurrence of this phenomenon. Also, it may be that increasing interest in the bacteriology and pathology of resected tissues and their availability have contributed to the increasing incidence.

Several investigators have been concerned with this noncultural status of visible acid-fast bacilli, many proposing they are dead (Hobby *et al.*[8]),

*Presented in part before the American Clinical and Climatological Association, November 1, 1955, at Hot Springs, Virginia.

others claiming they are alive (Dubos[5], Hobby *et al.*[7], and Vandiviere, Willis and Gentry[16]).

This question of "life" or "death" of the tubercle bacilli is not paramount in all lesions. Many do follow normally expected patterns of behavior, whereby microscopically visible acid-fast bacilli produce living and virulent colonies.

In respect to these bacilli that are visible but not necessarily viable, the question naturally arises: Is this phenomenon entirely the result of normal body mechanisms and the physicochemical state of the lesion, or does the drug affect the normal body mechanism's capacity to produce these unusual results? Does the failure to grow represent inadequacy of present techniques to demonstrate life? If so, then this would not be a criterion for death. Modifications of the living processes of the bacilli may have made it difficult to recognize the inner status of these adaptable microörganisms. Significant reduction in metabolic activity could easily result from lowered O_2 tension, long-chain fatty acids, enzymes and other biochemical or physicochemical environmental influences. An extension of the normal incubation periods has been suggested previously as a means of obtaining growth with these difficult bacilli. Willis, Vandiviere and Gentry[17] used extension of incubation alone, and Hobby *et al.*[7] used extended incubation with a modification of classical techniques.

It is intended in this study to: 1) offer some relationships between these aforementioned findings; 2) propose certain possibilities as to why some bacilli reproduce normally, why others require adjustments before "life" is manifest, and why others never seem to revive; and 3) evaluate the possible interactive influences of drugs and the host with various type lesions.

Materials and Methods. Surgically removed specimens were examined and dissected by the anatomist immediately following the operation, using aseptic technique. Lesions were located by dissection along the bronchi. The contents of the cavities, tubercles, and other lesions were scraped, washed, and a portion of the wall removed, so that samplings were representative of the whole of the lesion. Precautions were taken to prevent transfer of material between lesions. Each sample was transferred straightway to the bacteriologist for microscopic, cultural and animal processing. After complete fixation the specimen was redissected and carefully re-examined by the pathologist and selected blocks removed. The gross findings were then compared with those observations made previously. All entries were verified on the basis of the prior criteria established for each lesion. Cavities were classified as of three types:

1. *Open:* Those classical in structure, with thick walls, with a patent bronchus, and containing air and caseum.

2. *Closed:* Those similar to (1) except for the absence of a bronchial communication.

3. *End-Stage:* Those considered the ultimate in open-healing, which may or may not have had a patent bronchus. They were clean, thin, slick, shiny-walled cavities described in detail in the preceding paper (I).

The other lesions, tubercles and tuberculomas, were classified according to appearance and size. The solid, caseous, necrotic lesions of less than 1 cm. were arbitrarily designated as tubercles and those 1 cm. or greater in diameter were considered tuberculomas.

Direct smears were made from each lesion prior to processing for culture or animal injection, or both. All specimens were processed by homogenization with 4% NaOH, neutralized and planted on Jensen and Holm's modification of Löwenstein's medium (Melvin *et al.*[11]). The usual and acceptable practice is to observe cultures for 6 to 8 weeks' incubation and report as positive or negative at this period. This has not been the practice on these resected specimens. All lesions discussed herein represent material that has been planted on culture media, incubated at 37.5° and observed at regular intervals for at least 6 months following the date of resection, and many have had 18 months' incubation and observation. Other techniques were used on many of the specimens such as that described by Hobby *et al.*[7], liquid medium with human plasma, and others, but none had produced significantly better results than the classical technique with extended

incubation. Therefore, those results are not included in this study.

Drug sensitivity tests were made on the original material from each specimen or each culture, or both, as soon as growth became apparent. For these tests the drugs were incorporated into Löwenstein's medium.

Results. This study embraces 48 open cavities, 22 closed cavities, 17 end-stage cavities as well as numerous tubercles, tuberculomas and granulation tissue from 84 patients. All patients had received antituberculosis drug therapy and bed rest for varying periods of time.

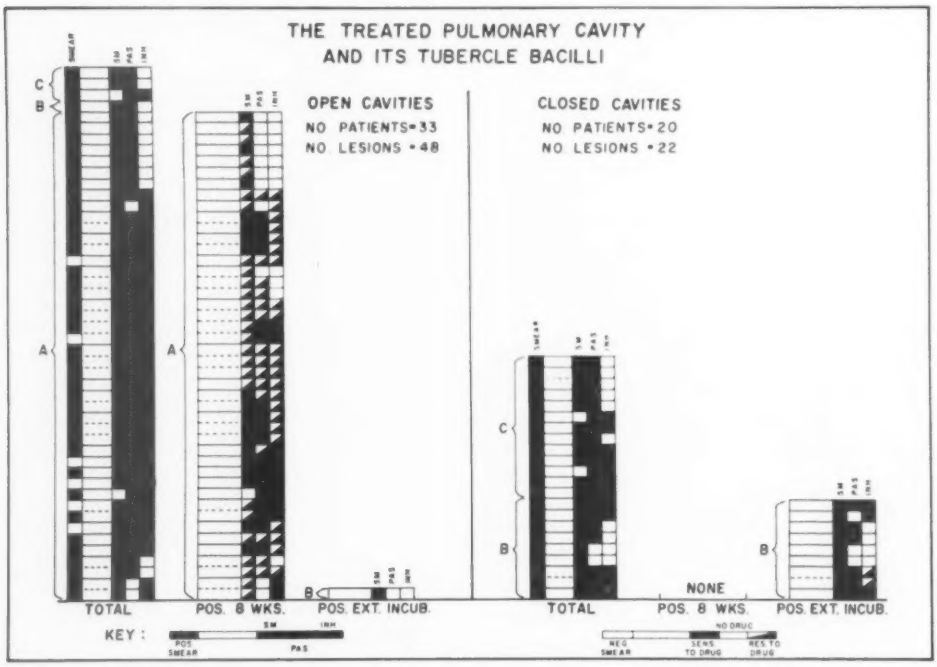

Fig. 1.—The bar graphs depict two types of classical cavities, the major physical difference being the status of a bronchial communication. Each "brick" of the bar represents a specific cavity. Dotted lines indicate the number of cavities per patient, each total space between solid lines representing one patient. A solid block under "smear" represents "positive." The solid blocks under "drug" illustrate the drug used prior to surgery. "A" are those specimens positive by culture, "B" those positive only on extended incubation, and "C" those still negative. The blocks in the cultured groups represent the drug susceptibility results.

Of the 48 open cavities (Fig. 1) 45 (94%) produced tubercle bacilli that were living and capable of reproduction, and all but one grew in the normal incubation period of 8 weeks. The one that grew on extended incubation required only approximately 3 months. These 33 patients varied considerably in the duration of chemotherapy prior to operation, all of them on combined therapy. Thirty-one of the 33 patients received streptomycin (mean 14.5 mos. ± 9.3); the same number received para-aminosalicylic acid (mean 8.8 mos. ± 5.9); and 21 of the 33 received isonicotinic acid hydrazide (mean 14 mos. ± 10.9). But in spite of this wide variation in chemotherapy prior to op-

eration, the tubercle bacilli recovered from this type of cavity, on 8 weeks' incubation, were, almost invariably (84%), resistant to one or more of the drugs used prior to removal of the tissue.

Results from the closed cavities (Fig. 1) were in startling contrast to those from the open cavities. Twenty-two of these closed cavities from 20 patients have been studied. Of these 22, not one has yielded bacilli showing any indication of viability in the usual 8 weeks' incubation time, but 9 (41%) did produce growth on extended incubation. The growth was manifest at periods varying from 3 to 10 months after planting onto media. The chemotherapy received by these 20 patients was as varied as that of the patients with open cavities (18 on SM with a mean of 8.8 ± 4.4; 18 on PAS with a mean of 7.1 ± 4.0 and 11 of the 20 receiving INH with a mean of 6.9 ± 2.5). In spite of the similarity in treatment, there were contrasting drug susceptibility results between cultures from the open and closed cavities. All but two of the lesions (from the same patient) revealed drug-susceptible bacilli and these two were only partially resistant to one of the drugs used prior to removal of the lesions.

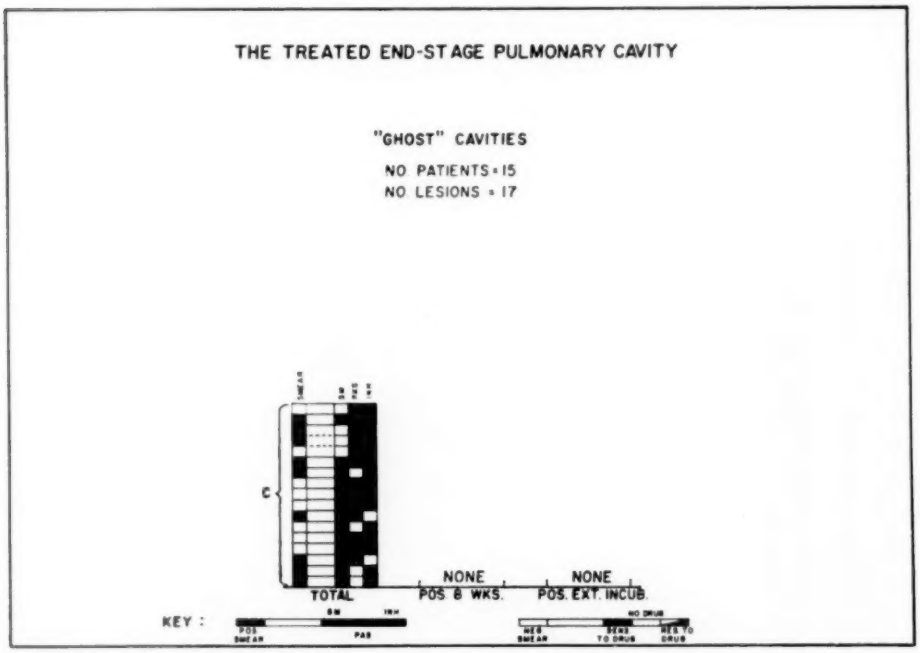

Fig. 2.—The same schema of data analysis was used as in Fig. 1. These end-stage cavities comprise the main thesis of the first paper. None of these specimens has produced growth on culture media or disease in animals.

It should be mentioned that microscopically visible acid-fast bacilli were present in 87% of the open and 100% of the closed cavities.

The end-stage ("ghost") cavities

(Fig. 2) and their pathological development were discussed at length in the preceding paper. Again, the bacteriological, as well as the pathological, data suggest strongly these to be the end-stage cavity. From these 17 end-stage cavities of 15 patients, two aspects predominate: 1) fewer cavities were positive microscopically, but even though acid-fast bacilli could be demonstrated in 9 (53%) only one to five bacilli could be demonstrated per microscopic slide. This is certainly less in total number than the open cavities (one to five per field) or the closed cavities (1 per 20 to 25 fields) discussed above; 2) even when bacilli were present, none grew, even after periods of incubation extending up to 2 years.

The data from tubercles and tuberculomas are given in Fig. 3. In the tubercles fewer smears were positive (73%) than in the open and closed cavities, but more were positive than in the "ghost," or end-stage cavities. The tuberculomas were microscopically more similar to the closed cavities but not so culturally. Very few (6% of the tubercles and 15% of the tuberculomas) of these lesions produced growth with either 8 weeks' or extended incubation. The bacilli that grew from these few tubercles did so in 8 weeks. The difference between the two periods of incubation was not significant for the tuberculomas.

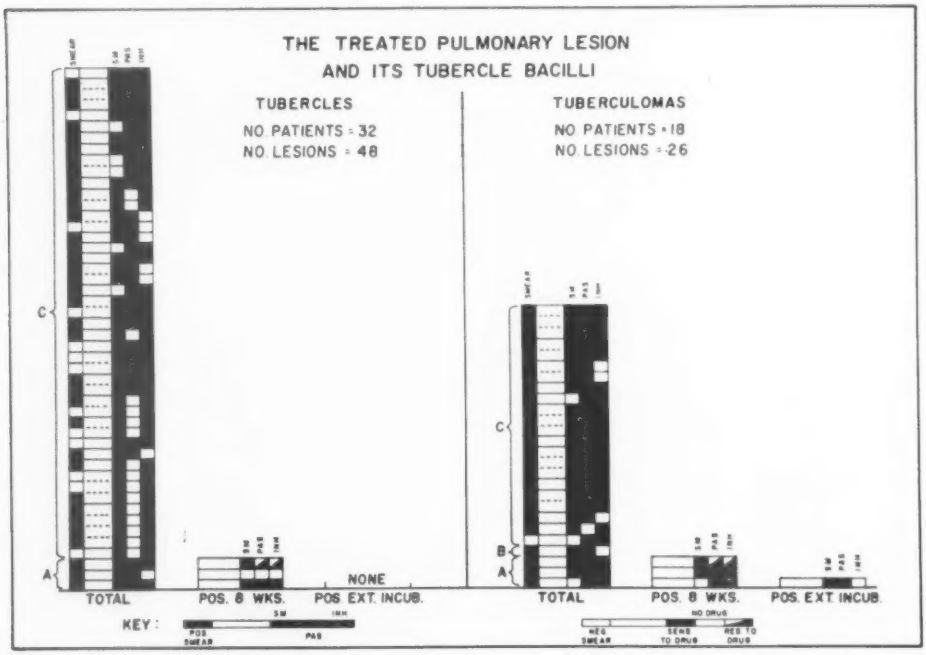

Fig. 3.—The same schema applies as in Fig. 1. These two series are the same type lesion pathologically, the size being the only criterion for distinguishing the tubercles (<1 cm.) and tuberculomas (1 cm. or >1 cm.).

Discussion. ON THE MATERIAL FROM THE OPEN CAVITY (Fig. 1). It appears that the open cavity offers ideal growth

conditions, such as the free flow of air and body fluids necessary to maintain tubercle bacilli in a relatively high state of metabolic activity. Thus when materials from these open cavities are removed and placed on media, the potential growth would be expected to, and does, appear within the usual period of less than 8 weeks.

When a patient has had chemotherapy, it is well known that drugs enter the cavity and its wall (Barclay[1] and Steenken, D'Esopo and Wolinsky[14]), but the drug incorporated in the body fluids probably enters the cavity at erratic intervals and in varying degrees of concentration. This should provide within the cavity conditions similar to those one would establish in the laboratory to develop resistant strains. Thus the drug would probably have a great deal of influence on the bacilli in the open lesion. If so, the drug effect would be either lethal to the bacilli or would force them to develop resistance to the drug and continue life and a normal metabolic state. Apparently this is exactly what occurs. Those that were capable of reproduction on artificial media demonstrated growth within 8 weeks and were, in general, resistant to one or more of the drugs. As to the lethal effect on tubercle bacilli, it seems that very few open cavitary lesions are actually free from viable bacilli, with the exception of those cavities that reach the end-point of healing, as exemplified in the "ghost" or end-stage cavities.

ON THE MATERIAL FROM CLOSED CAVITIES (Fig. 1). In the closed cavities, growth conditions are far from ideal. Media and oxygen, which Novy and Soule[12] demonstrated to be necessary for multiplication of tubercle bacilli *in vitro*, are in short supply. Lactic acid formation from glycolytic metabolism, long-chain fatty acids released by enzymatic action, and normally bacteriostatic tissue substances may be abundant in this type of lesion. All of these factors could be responsible for a reduction of metabolic activity in tubercle bacilli. Certainly, bacilli may be cultured from these lesions in fewer instances than from open lesions. This reduction could make the demonstration of viability of the tubercle bacilli extremely difficult, even without the influence of drugs. Also, the normally inhibitory concentrations of drug might fail to affect tubercle bacilli existing at such a low level of metabolic activity. If this state of dormancy lasted long enough, the normal effect of host resistance would be sufficient to reduce the total number of bacilli in the cavity (Canetti[3]). This could, with sufficient time, reduce the viable units, finally leading to sterilization of the cavity.

In these lesions fewer bacilli are found microscopically, per examined specimen, than in open, exudative lesions. Not only are the bacilli less in number but many acid-fast granules are seen. These facts are interesting and, obviously, have some significance but certainly one bacillus per 20 fields is still a sufficient number to give a highly positive culture if they were metabolically active.

Apparently the lesion which has precipitated the greatest concern among investigators is this closed cavity. Here, life or death is most difficult to establish. With the data from classical open cavities, it seems obvious that the bacilli are living. The results from the end-stage cavities suggest almost as emphatically, death. But closed lesions are debatable. It would be of unlimited value if bacteriologic techniques of viability testing could be accomplished on the bacilli as they occur in lesions. Such is not the case, and conclusions are retrospective at best. However, it does seem significant

that the closed cavities were the group in which extended incubation proved its value. The long incubation prior to manifest growth and the fact that the majority of cultures were still sensitive to drugs infer apodictic information concerning the tubercle bacilli: 1) the bacilli were in a low metabolic state and thus needed a period of readjustment; 2) the microörganisms were in such a state of metabolism and environment that drugs were ineffective.

ON MATERIAL FROM END-STAGE ("GHOST") CAVITIES (Fig. 3). These cavities contained very few tubercle bacilli and they failed to grow regardless of the manner of treatment or the duration of the incubation period. It is suggested that this remaining cyst is the combined result of efficient drug therapy and host resistance. Pathologically and bacteriologically, it is the end-stage of cavity healing. Yet clinically, it leaves much to be desired so long as the cavitation, and potential disaster area, remains for future secondary infection.

ON GENERAL CLINICAL IMPLICATIONS. The pathological findings in the previous paper and the bacteriological data given in this one present valuable basic information that should assist in answering the following oft-raised and vital clinical questions:

(1) Does the increasing incidence of end-stage cavities with patent bronchi imply that surgical intervention may become less frequent? On the contrary, may it with equal justification be held that removal of such areas will be desirable in anticipation that they could become the seat of troublesome and recurrent "cystic," nontuberculous infection? Or could it be that collapse therapy might lead to closure of these areas on the basis that the walls should collapse easily and their surfaces adhere and, thus, the seat of future "cystic" disease be removed?

(2) Classical caseous and thick-walled open cavities have produced a high incidence of drug-resistant tubercle bacilli. Does this stress the need of earlier operation, so that bacilli will still be susceptible to at least one major drug at the time of operation?

(3) Do these results re-emphasize the obvious importance of using the most effective drug (INH) as early as possible in the course of the disease? This inference is based on the manifest restraint on tubercle bacilli, the resulting reduction in caseum and the enhancement of collagen formation with localization of infection by the host. This interactive sequel results in the salvage of pulmonary function.

(4) Encapsulated caseous lesions comprising closed cavities, granulation tissue, tuberculomas and tubercles are readily diagnosed by Roentgen ray. They yielded 98% positive smears but only 29% viable bacilli, and 75% of these were susceptible to drugs. Again, the pertinent question is raised: In patients with this type of disease, is surgery the treatment of choice?

Summary. 1. This is a study that involves pathological and bacteriological investigation of pulmonary tissue removed surgically in the course of the treatment of tuberculosis. In it there were 48 open cavities, 26 closed cavities, 17 end-stage cavities and other lesions from 84 patients. All patients had received combination chemotherapy of varying duration.

2. From 48 open cavities, 44 (92%) produced positive cultures which grew in 8 weeks. One culture required 3 months to grow. The cultures were, in general, resistant to one or another of the major drugs.

3. From 22 closed cavities, no bacilli grew on culture within the usual 8-week period. In 9 instances (41%), cul-

tures grew on extended incubation from 3 to 10 months.

4. From 17 end-stage cavities, bacilli were found microscopically in 9, but none grew on culture, even on extended incubation.

These bacteriological and pathological (Paper I) data demonstrate obviation of the tubercle bacilli in certain lesions. This allows the normal body mechanisms and physicochemical status to produce the end-stage cavity.

The closed cavity with its hibernating bacilli is apparently the result of normal body mechanisms with little drug effect manifest within the cavity. It was in this type of lesion that extended incubation demonstrated its greatest value by increasing the propagability of the latent bacilli.

A high percentage of the classical open cavities revealed rapid growth and the bacilli were generally resistant to drugs. These are interpreted as drug failures insofar as the cavity and its bacilli are concerned.

These suggestions indicate eloquently that the whole story is not known, and, if proper enzymes (Pope[13]) or further improvements of techniques are introduced, more of these bacilli that are "dead" may actually be alive. One type of lesion (closed cavities) has revealed bacillary life where the fact of viability was doubtful. There may be other instances yet unknown. There are still bacilli that can be seen but do not grow with this technique. What will happen to them in the body? Will modified environmental conditions bring them to life? What is the future fate of these adapted tubercle bacilli?

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(Interlingua on page 56)

THE SERUM ALDOLASE LEVEL IN ACUTE MYOCARDIAL INFARCTION

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The glycolytic enzyme, aldolase, was first demonstrated in the serum of rats by Warburg and Christian[17]. They observed that it was consistently elevated in rats with large tumors. Employing a new method for the assay of aldolase, Sibley and Lehninger[12,13] confirmed these original observations and extended the study to a series of normal human subjects as well as patients with malignant neoplasms. They found that 20% of the persons with malignancies had a significantly increased serum level of this enzyme. Recently, increased serum aldolase activity has been demonstrated in a variety of conditions including pulmonary infarction, peripheral gangrene, severe pneumonia, hemorrhagic pancreatitis, severe hemolytic anemia, malignancy, acute hepatitis, as well as in experimental liver necrosis[3,14,15]. On the other hand, it has also been reported that the decrease of aldolase activity found in striated musculature of patients with progressive muscular dystrophy is associated with a concomitant increase of this enzyme in serum[4,10]. It was shown similarly that experimental nerve transection is followed by an increase in serum aldolase in conjunction with a decline in the activity of this enzyme in muscle tissue[2,5]. Since aldolase is normally present in both skeletal and heart muscle, it seemed reasonable to expect a hyperaldolasemia in human myocardial infarction and possibly in experimentally induced coronary occlusion. The release of this intracellular enzyme from damaged cells has been proposed to be the source of increased serum aldolase[14]. Such assumption should also permit the establishment of a semiquantitative correlation between the extent of myocardial necrosis and the serum aldolase level. This hypothesis prompted the present experiments intended to determine whether increased serum aldolase activity could be demonstrated in dogs subjected to ligation of the coronary arteries at various levels. Furthermore, preliminary clinical studies were initiated to investigate the applicability of the experimental data to human myocardial infarction.

Material and Methods. A. Twelve mongrel dogs, weighing from 15 to 20 kg. each, were subjected to a ligature of the descending branch of the left coronary artery below the bifurcation of the left main artery. This was considered a high ligation. In a second group of 10 dogs a suture was placed just below the origin of the septal artery from the descending ramus of the left coronary artery. This was termed a low ligation. In an other series of 10 control dogs a sham operation was carried out which was identical with the actual procedure in the other animals except that the coronary arteries were not violated. After intravenous sodium-pentobarbital anesthesia in a dosage of 30 mg. per kg., an endotracheal tube was inserted

under laryngoscopic guidance and attached to a mechanical respirator. Under aseptic conditions the left side of the chest was explored through the fourth intercostal space whereby the left atrium and the left coronary artery were adequately exposed. The ligatures were then placed at the prescribed sites around both artery and vein or following isolation of the artery alone.

Serum aldolase determinations were carried out in all animals prior to operation and daily thereafter for at least 3 days. In two animals, serum aldolase determinations were carried out preoperatively and for 7 and 8 consecutive hours, respectively, after high coronary ligation. All animals were sacrificed within 3 to 10 days following coronary artery ligation and the hearts were examined grossly and microscopically to substantiate occlusion of the vessel and to evaluate extent of necrosis and the phase of healing.

Tissue aldolase activity of intact and necrotic heart muscle was studied in 14 animals of which 7 had been subjected to coronary ligation. Normal heart muscle was removed from the posterior wall of both ventricles as well as from the anterior wall of the right ventricle. Similarly, normal or infarcted myocardium was obtained from the anterior wall of the left ventricle at various time intervals following the operation. Serum as well as tissue aldolase determinations were carried out according to the method of Sibley and Lehninger[12].

B. In preliminary clinical studies on 8 patients with acute myocardial infarction and 5 cases diagnosed as coronary insufficiency, verification of the experimental data was sought. Daily determinations of the serum aldolase were carried out.

Results. A. The preoperative serum aldolase level of all animals studied in this series was in accord with that previously established as normal for this species, 15.71 units per ml. (S.E. $\pm$ 1.01)[2]. The control animals showed a rise to 39.7 units per ml. on the first day after sham operation (Fig. 1). This value remained at a plateau level for the next 24 hours, at the end of which time it was 39.1 and declined subsequently to 35.1, 24.0, and 18.1 units per ml. three, four and five days after surgical intervention. Animals with low coronary ligation exhibited a sudden rise of the mean serum aldolase level to 61.2 units per ml. 24 hours and 62.1 units per ml. two days after coronary ligation. From then on, the values decreased to 44.0, 26.4, and 7.8 units per ml. on the third, fourth, and fifth days after operation respectively. The animals subjected to a high coronary ligation had the highest mean serum aldolase level observed in this study. It reached a peak of 95.4 units per ml. 24 hours after operation. The mean value declined to 66.1, 61.8, 35.2, and 20.3 units per ml. on the second, third, fourth, and fifth days after operation. None of the animals displayed any complications during this interval. The hourly serum aldolase determinations in two animals with high coronary ligation revealed a significant rise within 2 hours after operation. The values rose steeply during the observation period of 7 and 8 hours, respectively (Fig. 2.).

The mean tissue aldolase activity of normal heart muscle, regardless of its topographic origin, was 12.9×10^4 units per gm. of noncollagenous protein (NCP). The corresponding mean values of infarcted myocardium were considerably less, namely 3.6×10^4 units per gm. of NCP.

Gross inspection of hearts with high coronary ligation disclosed a wedge-shaped, yellowish, soft, well-demarcated area of necrosis which was observed up to the fifth day. In these animals, the infarct extended from the ligature at the base of the heart to the apex and usually involved almost the entire thickness of the left ventricle in an area of approximately 4.5×3 cm. In the specimens with low ligation, a similar type of altered tissue replaced the heart muscle but involved a correspondingly smaller area of about 1.5×1.5 cm. Seven days after experimental coronary closure, large areas of gray-white, moderately firm, vascularized tissue were noted. Microscopic

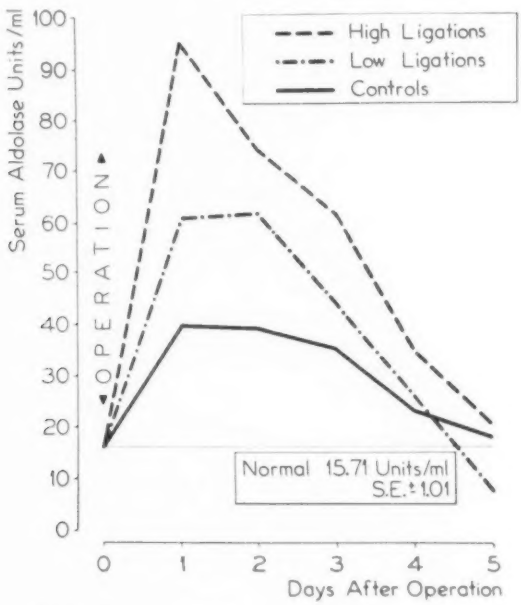

Fig. 1.—Mean serum aldolase levels of 10 dogs with high coronary ligation, of 10 dogs with low coronary ligation, as well as of 10 sham-operated control animals.

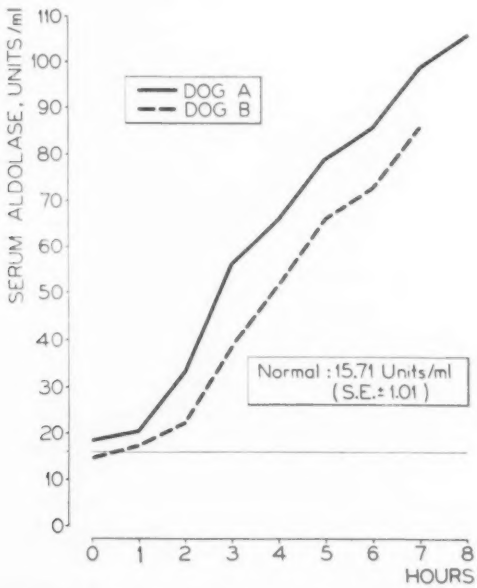

Fig. 2.—Hourly postoperative serum aldolase levels of 2 dogs with high coronary ligation.

studies of all dog hearts with coronary ligation disclosed the presence of extensive myocardial necrosis whenever the animals were sacrificed before the seventh day. Granulation tissue, in varying stages of healing, was seen when the animals were killed between the seventh and the tenth days.

B. The established normal value of serum aldolase in human adults is 7.14 (S.E. ± 0.73) units per ml. In the 8 cases of acute myocardial infarction, the serum aldolase rose to reach peak values ranging from 29 to 112 units per ml. within 24 to 48 hours after onset of initial symptoms of coronary occlusion (Fig. 3). It rapidly declined to normal levels on the fifth day of the disease. In view of the preliminary nature of the clinical study no statistical data were established. One patient whose serum aldolase level reached 112 units per ml. expired within 36 hours after the onset of clinical manifestations. Another patient with an aldolase value of 78.6 units per ml. expired after onset of infarction. Electrocardiographically, proof of an acute infarction was established in all instances. Patients with a moderate aldolase elevation, generally, fared better than those with very high serum aldolase levels. None of the 5 patients with coronary insufficiency displayed increased serum aldolase activity within an observation period of up to 6 weeks.

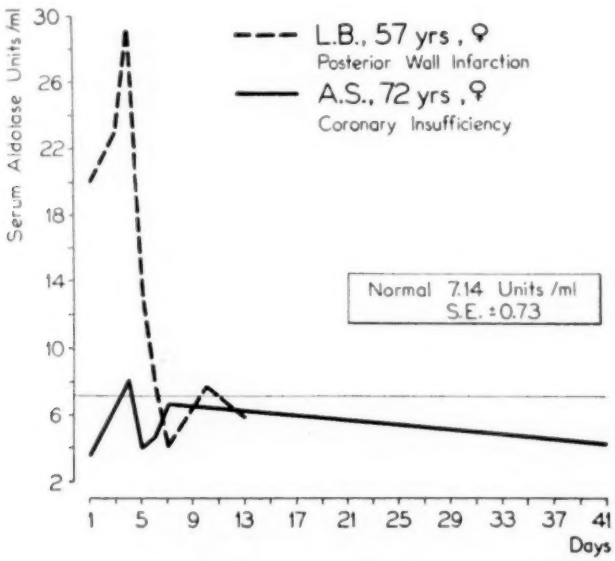

Fig. 3.—Daily serum aldolase levels in a patient with acute myocardial infarction and in a patient with coronary insufficiency.

Discussion. In a recent survey of the aldolase level in sera of approximately 900 patients with a wide variety of diseases, it was observed that abnormally high levels of this enzyme occurred rather infrequently and were usually associated with acute and extensive tissue injury such as occurring in cancer, leukemia, extensive peripheral gangrene, acute hemorrhagic pan-

creatitis, large pulmonary infarcts, or acute hepatitis[14]. Similarly, in a large number of patients with progressive muscular dystrophy, a considerable increase of this enzyme was observed[4,11]. It is believed that in some of these conditions the elevated serum aldolase levels are due to extensive tissue destruction leading to excessive liberation of this enzyme to such a degree that it cannot be cleared rapidly enough from the circulation[14]. On the other hand, the sustained increase of this glycolytic enzyme in serum, as reported in patients with slowly evolving progressive muscular dystrophy may be the result of release of enzyme from continuing striated muscle degeneration.

The rapid rise of serum aldolase levels as observed in human myocardial infarction and in dogs with experimentally produced coronary occlusion, seems to bear out the previous assumption that myocardial necrosis leads to liberation of this enzyme with subsequent hyperaldolasemia. Adverse environmental conditions in tissue slice experiments, (for example, insufficient amounts of oxygen or inadequate amounts of glucose) lead to prompt liberation of tissue aldolase[16]. These observations have been made both from fresh slices of the Walker carcinosarcoma and from normal liver. The same phenomenon was confirmed further by recent work in which the production of focal hepatic necrosis in the rat by inhalation of carbon tetrachloride resulted in a pronounced, but transient elevation of serum aldolase[15].

It is of particular interest that the animals with low coronary artery ligation attained a considerably lower aldolase peak serum level than dogs with high ligation. It thus appears that, in experimental myocardial infarction, a semiquantitative relationship exists between the serum aldolase level and the amount of necrosis in the heart muscle. The slight rise in serum aldolase in dogs subjected to the sham procedure, was attributed to skeletal muscle destruction attending surgical manipulation.

Preliminary studies of patients with acute coronary occlusion have confirmed the experimental data inasmuch as the aldolase levels were higher in those individuals who were clinically more severely affected by the coronary occlusion. Furthermore, our studies clearly indicate an inverse relationship between the amount of aldolase in myocardium and serum after coronary ligation. The necrotic tissue contained a significantly decreased aldolase concentration as compared with normal heart muscle.

We have previously reported a semiquantitative relationship between the extent of myocardial necrosis and the plasma fibrinogen concentration in experimental coronary occlusion[18] and human myocardial infarction[9]. While the elevation of fibrinogen level, particularly in man, extends over a period of more than 2 weeks, corresponding enzyme values tend to return to normal within 4 or 5 days at most. This seems to apply to both serum aldolase, as described herein, as well as the recently reported SGO-transaminase[1,6,7,8]. On the other hand, enzyme values tend to rise very early during the illness preceding the increase of other blood constituents, for example, fibrinogen, C-reactive protein, mucoproteins, globulins, and so forth. Whereas the serum aldolase levels rose significantly in all 8 patients with acute myocardial infarction included in this study, electrocardiographic abnormalities in two of these patients appeared 24 and 48 hours respectively after the concentration of this enzyme rose.

In coronary insufficiency, however, neither fibrinogen[9], serum aldolase nor SGO-transaminase[1,8] exceed the range

of normal values. The persistence of normal values in this condition is taken to indicate the absence of myocardial necrosis and may be used in the differentiation of coronary insufficiency from myocardial infarction even when electrocardiographic studies yield ambiguous results.

Because of the simplicity of the procedure, it is believed that the determination of the serum aldolase may provide an additional useful tool in the early diagnosis of acute coronary occlusion. Our observations, experimental and clinical, seem to indicate that it may well supplement electrocardiographic studies. Particularly when carried out in conjunction with determinations of SGO-transaminase and plasma fibrinogen, it may provide a method of estimating the extent of myocardial necrosis and thus contribute to the clinical evaluation with regard to therapy and prognosis.

Summary. 1) Thirty-two mongrel dogs were subjected to pericardiotomy. The descending branch of the left coronary artery was then ligated in 12 animals just below the bifurcation, thus producing a high ligation. In 10 animals a low ligation was performed. The remaining 10 animals served as controls.

2) Serum aldolase levels were studied daily in all animals and at hourly intervals for 7 and 8 hours, respectively, in 2 dogs with high coronary ligation.

3) There was a considerable and rapid rise of the serum aldolase in all coronary-ligated dogs postoperatively. A semiquantitative relationship between the area of myocardial necrosis and the serum aldolase was established.

4) In a preliminary clinical study, 8 patients with acute myocardial infarction displayed a considerable rise of the serum aldolase level in accordance with the approximate severity of the clinical course. In 5 patients with coronary insufficiency the serum aldolase remained normal.

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(Interlingua on page 92)

CLEARANCE OF RADIOACTIVE IODINE FROM THE LOWER EXTREMITIES OF PATIENTS WITH MYOCARDIAL INFARCTION*

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In the course of a study on the clearance of various radioactive isotopes from muscle, it was found that patients who had had previous myocardial infarctions cleared tracer amounts at a much slower rate than normal subjects[1]. The present study is a further investigation of clearance determinations from thigh muscles of patients with recent myocardial infarctions. Serial determinations were begun as soon after the acute episode as possible and extended into the period of convalescence.

Materials and Method. Thirty-five patients with acute myocardial infarction were studied. Muscle clearances were done as soon as possible after admission to the hospital and at intervals of 3 to 7 days until discharge or death of the patient. None of the patients studied had congestive heart failure. Venous pressure and circulation times were all within the normal range, except for patients in shock who were treated with intravenous norepinephrine (Levophed). In these patients, clearances were done during the administration of Levophed.

Tracer amounts of carrier-free I^{131} in normal saline, ranging from 0.5 to 1.0 microcurie, were used. Radioactive iodine was chosen since it has been shown that it can be used interchangeably with NA^{24} and K^{42} [1]. An area of the thigh, about 10 cm. above the knee, was the injection site. A jet injector was used for the injection of the tracer.† Immediately following the injection, a scintillation tube was lowered over the injection site and the disappearance of the injected radioactive tracer was recorded on a counting rate meter and Esterline-Angus paper. The background of the tube was about 1000 counts per minute

*Supported by grants from The Los Angeles County Heart Association, The Riverside County Heart Association and the R. P. Scherer Corporation, Detroit, Michigan.

**Present address: Army of the United States.

†Hypospray, R. P. Scherer Corp., Detroit, Michigan. Results of measurements of the disappearance of jet-injected tracer amounts have been shown to be more reproducible than those obtained by needle injections[1]. The solution of I^{131} is loaded into metapules under aseptic conditions. The jet-injected solution penetrates into the muscle. The injection is quite painless.

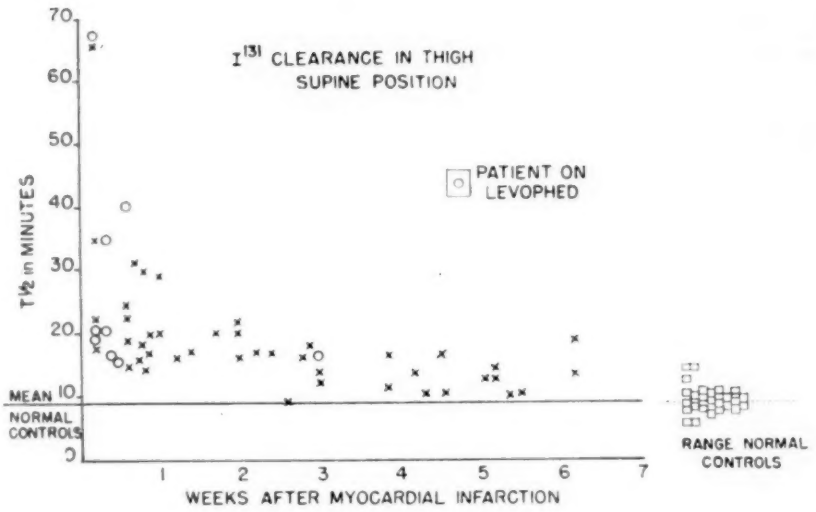

Fig. 1.—Results of 52 clearances of I^{131} from thigh muscle in 35 patients with myocardial infarctions.

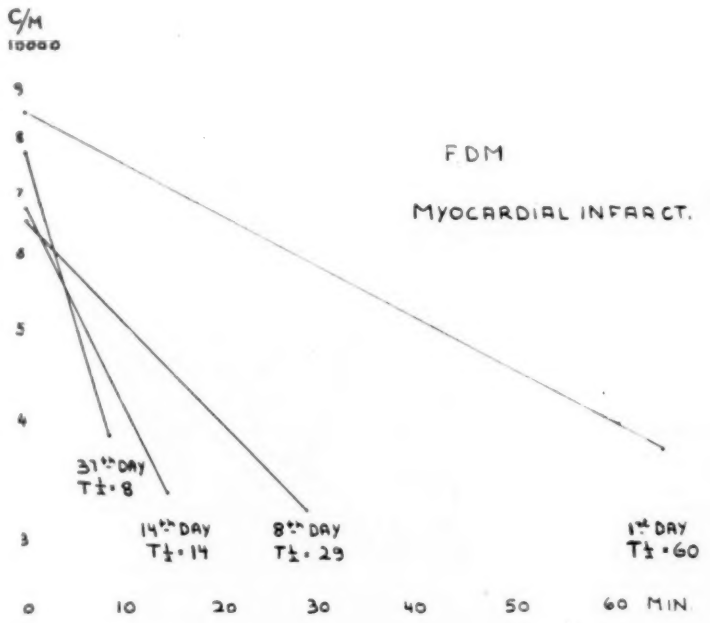

Fig. 2.—Serial clearances of I^{131} from thigh in a patient with myocardial infarction.

and the activity of the injected radioactive tracer in the range of 8000 to 20,000 counts per minute. The disappearance of the tracer was recorded either until half of the radioactivity had disappeared from the injection site, or for a period of 30 to 60 minutes if the disappearance was slow.

In the beginning of the study, clearances were done at the bedside with the patients supine. One of the patients, whose clearance time in the supine position had become normal in the 6th week after a myocardial infarction, was found to have a greatly prolonged clearance in the sitting position. Thereafter, most

TABLE 1.—EFFECT OF POSITION OF I^{131} HALF-TIME IN MINUTES

Weeks After Myocardial Infarction

	1		*2*		*3*		*4*		*5*		*6*	
Patient	*Supine*	*Sitting*	*Supine*	*Sitting*	*Supine*	*Sitting*	*Supine*	*Sitting*	*Supine*	*Sitting*	*Supine*	*Sitting*
1	23	40										
2	31	∞	20	24							15	17
3	19	31			16	20						
4	20	25			18	22			10	9		
5	30	45							10	9		
6			20	26							17	17
7	66	∞	29	∞	16	26			9	10		
8											10	17
9											12	24

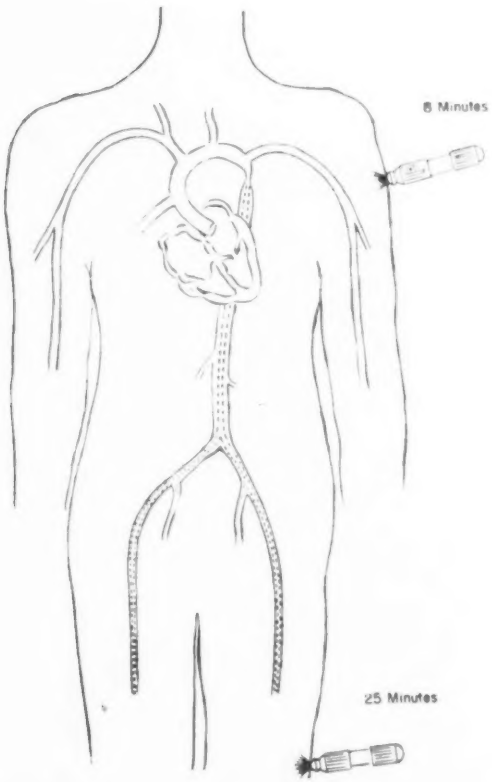

Fig. 3.—I^{131} clearance from arm and thigh in a patient with coarctation of the aorta.

of the patients were tested first in the supine position and immediately thereafter, sitting up with the legs hanging over the side of the bed and their back supported by pillows. The clearance of the same jet-injected dose of I^{131} was measured in both positions.

Results. Figure 1 shows the clearance half-times of 28 healthy control subjects and of 52 tests on 35 patients with myocardial infarction.

HEALTHY CONTROL SUBJECTS. The disappearance of half the injected tracer was in the range of 6 to 14 minutes with a mean of 9 minutes.

PATIENTS WITH MYOCARDIAL INFARCTION. The disappearance of the injected tracer in the supine position was in the range of 9 to 67 minutes.

It is apparent that in the course of convalescence the clearance times approach normal. Several patients were in shock, sometimes due to an additional myocardial infarction and were given intravenous Levophed.

Figure 2 shows the typical course of events in a patient with a recent myocardial infarction.

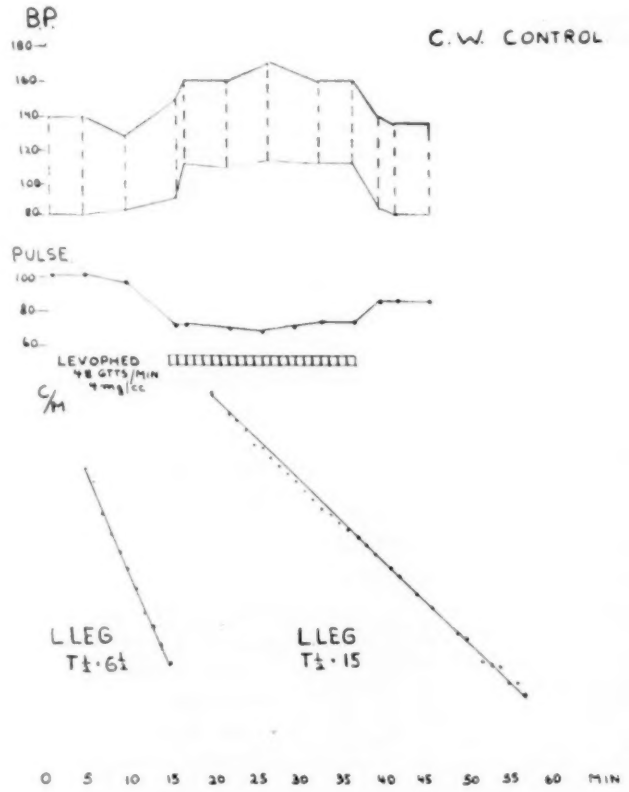

Fig. 4.—Effect of an intravenous infusion of norepinephrine on the pulse, blood pressure and clearance of I^{131} from the thigh of a healthy subject. Supine position. The clearance determination was done on the same jet-injected tracer dose of I^{131}.

Table 1 shows the changes in those patients in whom the clearance was determined both in the supine and sitting positions. It is apparent that in the first 2 weeks after myocardial infarction the clearance times are generally prolonged in the sitting position. This difference persists until the 5th week, although it was observed as late as 6 weeks after myocardial infarction and in some instances for longer periods.

Discussion. The mechanism of delayed clearance of tracer amounts of I^{131} from the thigh in patients with myocardial infarction is not clear. Although not proven at this time, it is suggested that the phenomenon demonstrated in this paper may indicate a decrease of the peripheral capillary bed due to either partial or complete vasoconstriction. Preliminary evidence in support of this hypothesis is offered by two different observations: (1) a patient with coarctation of the aorta had a clearance "half-time" of 8 minutes in the right arm and 24 minutes in the thigh (Fig. 3), and (2) intravenous infusions of norepinephrine cause a great delay of the peripheral clearance time (Fig. 4).

It is possible that the diminished cardiac output after myocardial infarction is followed by a compensatory reduction of the peripheral capillaries or arteriovenous anastomoses, or both. Whether it is mediated through humoral or neurogenic mechanisms, or whether the peripheral vascular bed is reconditioned after myocardial injury cannot be stated at this time. There is, however, considerable experimental evidence that there is no relationship between the peripheral radioisotope clearance and blood flow[3,5].

The greatly prolonged clearance in the sitting position, particularly after the return to normal of clearances in the supine position, indicates a disturbance of homeostasis not observed in normal subjects. It is unlikely that renal factors, such as sodium and water retention[4], could account for this finding since it occurs almost instantaneously after change from the supine to the sitting position.

Cardiac output has been shown to be decreased in the chair position[2]. Investigations in progress at this time will attempt to shed light on the relationship between delayed peripheral isotope clearance and cardiac output.

Summary. 1. The clearance of tracer amounts of radioactive iodine from the thigh, injected by Hypospray, was measured in patients with recent myocardial infarction throughout convalescence.

2. Greatly prolonged clearance times were found in the first few weeks after infarction. The clearance became normal in the 6th week in the majority of patients.

3. In a number of patients, the clearance remained prolonged in the sitting position once it had returned to normal in the supine position.

4. These findings suggest a diminution of the peripheral capillary bed, possibly due to diminished cardiac output.

ACKNOWLEDGMENT: The authors wish to thank Drs. Benedict Cassen and Morton Lee Pearce for valuable suggestions.

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SUMMARIO IN INTERLINGUA

Clearance de Iodo Radioactive ab le Extremitates Inferior de Patientes con Infarcimento Myocardial

1. Le clearance de quantitates traciator de iodo radio-active ab le femore, injicite per hyposparsion ("Hypospray" [R. P. Scherer Corp.]), esseva mesurate in patientes con recente infarcimentos myocardial durante le integre curso de lor convalescentia.

2. Durante le prime septimanas post le infarcimento un grande prolongation del tempore de clearance esseva constatate. In le majoritate del patientes le clearance deveniva normal durante le sexte septimana.

3. In un numero de patientes le clearance remaneva prolongate in position sedente post que illo habeva retornate al norma in le position jacente.

4. Iste constatationes suggere le occurrentia de un reduction del capillares peripheric, possibilemente in consequentia de un reducite rendimento cardiac.

SUMMARIO IN INTERLINGUA

(See page 20 for original article)

Le Tractate Lesion Pulmonar e su Bacillo de Tuberculose

I. Pathologia e Pathogenese

Le pathologia de tuberculose pulmonar se trova in stato transformatori. Es presentate un summario de ille processos transformatori, basate super le observationes de nostre laboratorio e le constatationes de altere autores. Iste phenomeno es explicate per le extense uso de progressivemente plus efficace methodos chimotherapeutic. Pathogeneticamente le phenomeno representa un modification del classic responsa de inflammation e reparatura. Le duo currentemente plus efficace drogas, streptomycina e isoniazido, ha le capacitate de attaccar le bacillo tuberculotic directemente. Per iste action illos contribue fortemente al prevention del multiplication del bacillos, causa un relentation del processos metabolic e permitte assi le complete destruction del micro-organismo. Le conclusiones pathologic presentate in iste articulo ha un base indirecte. Le constatationes bacteriologic que es presentate in un secunde articulo se deriva ab le mesme datos e representa un material de valor additional. Nostre observationes indica que, in tanto que plus competente drogas va esser discoperite e introducite in uso general, le pathologia de tuberculose pulmonar va experientiar un ancora plus frappante metamorphose. Per consequente, un re-evalutation del currente conceptos, tanto medico- como etiam chirurgico-therapeutic, pare indicate.

DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF EOSINOPENIA IN ACUTE MYOCARDIAL INFARCTION

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The observation that eosinopenia may be found in febrile diseases, in the cachectic and in the moribund state was made more than 60 years ago[13]. Naegeli, in his textbook of hematology, published 1912, gives severe infections, intoxications and surgical procedures as the cause of decrease of the number of circulating blood eosinophils[10]. Selye found eosinopenia to be one of the characteristic features of the "alarm reaction"[1], and evidence has been presented that this effect partly is mediated by the adrenal cortex[4]. It has been shown to be present in a wide variety of clinical conditions involving stress.

Thus a decrease in number or a complete disappearance of the circulating blood eosinophils also has been found to be characteristic of the early phase of acute myocardial infarction[6], and recently an extensive study of adrenal functions, including serial eosinophil counts, has been published[5]. The author of the present article suggested in a preliminary report, in 1951, that the eosinophil count may prove useful in the diagnosis and prognosis of acute myocardial infarction[7], and later this subject has been discussed by other authors[2,3]. Ellestad and Reed found a drop in eosinophils to 20 per mm.^{3} or below for 2 to 6 days in 17 cases with electrocardiographic evidence of transmural infarction, staying at 50% below estimated normal for an average of 5 days. Thirteen cases diagnosed as subendocardial infarction also dropped to 20 or below, but the eosinopenia in these cases had an average duration of 2 days shorter than the previous group. The authors stated that, in the presence of equivocal electrocardiographic findings, "eosinopenia may well be of value as an adjunct in diagnosis." Feldman *et al.* studied 51 patients with the suspected diagnosis of myocardial infarction, 23 of whom had unequivocal signs of this disease, while it was considered probable in an additional 5 patients. They found 3 patients with eosinophil counts above 50 per mm.^{3} on the first 2 days following the onset of the disease. The authors concluded that "the eosinopenia was not encountered consistently enough to be of differential diagnostic significance." They found no consistent correlation between the degree and duration of the initial eosinopenia and either the clinical severity of the disease or the ultimate prognosis. Linden, in studying the prognostic aspects of myocardial infarction, found a mortality of 40% among 35 patients with eosinophil counts below 50, as against 18% among 28 patients with higher counts[9]. It is not evident from this publication whether the counts were made in the early phase of the disease or not.

The purpose of the present investigations has been to re-evaluate this problem on the basis of a greater clin-

ical material. The work has been carried out at Lovisenberg Hospital from November, 1950, to December, 1952, and at Drammen Hospital from July, 1953, to December, 1954.

Material and Methods. A total of 149 patients with a diagnosis of myocardial infarction was studied. Only patients giving a history in which the onset of the disease could be accurately determined and where the admission to hospital did not occur later than the fifth postinfarction day were included. Seventy-two of the patients were admitted within 24 hours following onset, 43 on the second day, 18 on the third and the rest of the patients on the fourth and fifth days. The age and sex distribution are summarized in Table 1.

TABLE 1.—AGE AND SEX DISTRIBUTION

	Age						
	<40	*40–50*	*50–60*	*60–70*	*70–80*	*>80*	*Total*
Males	1	10	30	26	19	6	92
Females	1	1	7	26	19	3	57

The initial eosinophil count was made on admission and following this daily counts before breakfast were performed in a period up to 3 weeks. The eosinophil counts were made in counting chamber by Rud's or Randolph's method[11,12].

The normal eosinophil level is not definitively settled, and low counts may occasionally be found in normal individuals. In the present work, however, eosinophil counts above 50 per mm.^{3} have been considered normal.

The diagnosis of myocardial infarction was made in the usual way. Serial electrocardiographic tracings showing progressive changes characteristic of this disease were considered the most important single sign. The routine laboratory procedures included sedimentation rate and white cell count. The eosinophil counts were not taken into consideration in the diagnosis.

Eosinophil counts were also performed in 306 patients suffering from some of the diseases which may have to be considered when the diagnosis of myocardial infarction is made. In these cases the counts were made on admission or, in the case of anginal pain, not more than 48 hours after the acute attack.

Results. In the great majority of cases an early eosinopenia of 2 days' duration or more was found. In some cases counts were obtained as early as 1 or 2 hours after the acute onset of myocardial infarction, always revealing normal eosinophils. From the third to the fifth hour results were equivocal, but usually eosinopenia was found (Fig. 1). However, in the period from 5 to 48 hours, eosinopenia in our material has been a very consistent finding (Fig. 2). One hundred and thirteen patients had counts performed within this period and the majority, 100 patients, had initial counts below 20 per mm.^{3}, 11 had counts between 20 and 50 and only 2 patients had higher initial counts. An additional 3 patients, who on their first day had an eosinopenia, on the second day revealed normal values. Normal eosinophil counts thus were found in a total of 5 cases in this period. In three of these patients the lack of early eosinopenia may possibly be accounted for by preexisting eosinophilia or Addison's disease.

A man, aged 65, had on his first and second postinfarction day eosinophil counts of 19 and 94 respectively. The possibility of underlying eosinophilia was suggested by a count of 656 later in the course of the disease. The patient did not, however, reveal a history of hypersensitivity.

One additional patient, a man, aged 58, and with counts of 100 and 156 on the first 2 days, developed an eosinophilia with count of 738 after a week. Later this patient had symptoms of hypersensitivity to the anticoagulant

drug used (phenylinandione) with urticaria and agranulocytosis[8].

A 64-year-old man had on admission an eosinophil count of 38. Despite severe shock with death after 12 hours in hospital, this patient revealed increasing values of the eosinophil counts, 62 and 132. At necropsy an atrophy of the adrenal cortex was demonstrated.

For the remaining 2 patients revealing normal eosinophils in the early phase of the disease no explanation can be given. One of these patients had during the entire course normal tem-

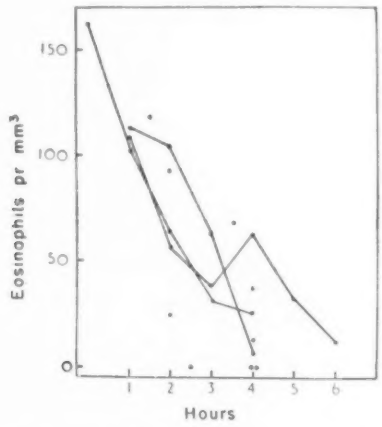

Fig. 1.—Eosinophil counts made during the first hours following an attack of acute myocardial infarction. The drawn lines represent serial counts in individual patients. The single points represent counts made in different patients.

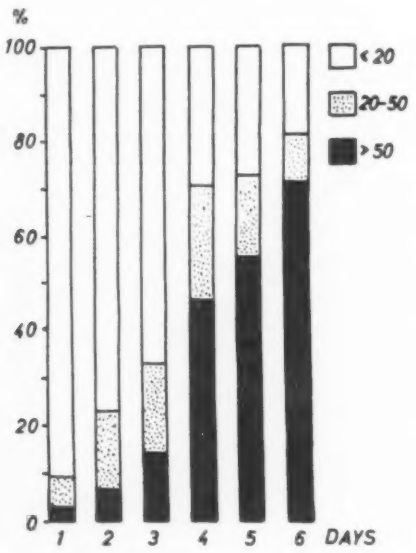

Fig. 2.—Eosinophil counts made on the first 6 days following acute myocardial infarction, expressed as percentages of the counts made on the respective days.

perature, sedimentation rate and white blood count, while the electrocardiogram showed progressive changes characteristic of acute posterior myocardial infarction.

On the third postinfarction day normal eosinophil counts were found in several patients, and 15% of the counts performed on this day were above 50. From the fourth day on, normal eosinophils were found very often (Fig. 2).

As for the subsequent pattern of the eosinophil curve the patients may be divided into two groups. A duration of the eosinopenia of less than 7 days was found in 81 patients, while prolonged eosinopenia, for 7 days or more, was encountered in 23 cases. It has been our impression that a correlation exists between the duration of the eosinopenia and the clinical course of the disease. Uneventful recovery was the usual course in the first group and only 2 of the 81 patients died. In the other group, revealing eosinopenia for more than a week, the patients very often ran an unfavorable clinical course with prolonged shock or congestive failure, and 16 of the patients died. The difference in mortality in the two groups, 2.5% as against 69.5%, is highly significant statistically.

The death rate was considerably lower in a group of patients revealing initial counts above 20, than in a group with eosinophil counts below this limit, 16.5% as against 39.5%. However, due to the small number of cases in the first group, the difference is not statistically significant. The total mortality of the entire group was 35%.

Eosinophil counts made in a variety of other diseases are summarized in Table 2. A severe eosinopenia very often was found in pneumonia, pulmonary embolism, acute congestive failure, cardiac arrhythmias and gallbladder disease. However, patients with uncomplicated angina pectoris most often revealed normal counts. This was shown to be true whether there was electrocardiographic evidence of heart disease or not, and was also true in a group of patients with anginal syndrome and a history of previous myocardial infarction. However, if the angina pectoris was complicated by signs

TABLE 2.—EOSINOPHIL COUNTS MADE IN DISEASES OF DIFFERENTIAL DIAGNOSTIC SIGNIFICANCE AS REGARDS ACUTE MYOCARDIAL INFARCTION

		Angina Pectoris		
Eosinophils	*Uncomplicated*	*Pathologic EKG*	*History of Infarction*	*Congestive Failure*
Below 20	0	2	1	11
20–50	5	3	0	21
50–100	17	15	18	10
Above 100	31	27	19	7

Eosinophils	*Pulmonary Embolism*	*Pneumonia*	*Congestive Failure*	*Gall bladder Disease*
Below 20	9	7	23	6
20–50	5	3	5	2
50–100	1	0	9	2
Above 100	0	5	7	1

Eosinophils	*Arrhythmias*
Below 20	13
20–50	1
50–100	7
100	3

of congestive failure the patients usually had a low eosinophil count.

COMMENTS. The diagnosis of acute myocardial infarction is based on the history, the clinical findings and an evaluation of the electrocardiographic changes. Nonspecific signs of disease, fever, elevated sedimentation rate and white cell count are used as adjuncts. In the early phase of the disease, the diagnosis may be very difficult. The first electrocardiographic tracings may not be conclusive, and fever and elevated sedimentation rate very often are absent on the first and second postinfarction day. An elevation of the white blood count may be of help during this period, but is an unreliable sign. It is not only nonspecific, but in our patients with acute coronary infarction counts below 8000 have been found as often as in 16% on the first day, 24% on the second day and 27% on the third day. We feel that the eosinophil count may be of some aid in this phase of the disease, and that in this respect it is superior to the total white cell count.

The problem of diagnostic significance of eosinophil cell counts has in this connection two different aspects: 1) To what extent does a normal count rule out the possibility of myocardial infarction?, and 2) To what extent does the finding of an eosinopenia indicate the presence of this disease?

1) A normal eosinophil count in the period from 5 to 48 hours following an attack suspected to be a coronary occlusion contradicts the diagnosis. Although it does not rule it out conclusively, exceptions are unusual. Only 3% of the counts made on the first day and 6% on the second day have been above 50 per mm.^{3}. Allergy, eosinophilia or adrenocortical insufficiency may account for some of the exceptions, but not for all. It may be that a small infarction occasionally does not call forth the necessary stimulation to the mechanism producing the usual eosinopenia of stress.

The results obtained on the third day have been more equivocal and 15% of the counts have been found to be normal. From the fourth day on, no conclusion as regards diagnosis may be drawn from a normal eosinophil count.

2) The eosinopenia of stress is a highly nonspecific phenomenon. The finding of a low count, therefore, is of no value in the differential diagnosis of coronary infarction as regards pneumonia, pulmonary embolism, cardiac arrhythmias, acute congestive failure, gallbladder disease or other diseases involving severe stress (Table 2). Uncomplicated angina pectoris, however, does not usually evoke eosinopenia, and the eosinopenia may thus be of some aid in the differential diagnosis of myocardial infarction as regards this disease.

The problem of prognosis of the myocardial infarction has lately been given more consideration than before. It has been maintained that a large group of patients, the so-called "good risk" cases, will stand a fair chance even untreated, and that only the "poor risk" cases should have anticoagulant therapy.

A number of signs have been considered characteristic of the "poor risk" group, and the conclusion to be drawn from the material presented here is that the finding of prolonged eosinopenia, for a week or more, also will qualify the patient for this group. The practical importance of this sign is, however, limited, as usually the decision regarding therapy has to be taken in a much earlier phase of the disease.

Summary. Eosinophil counts were performed in 149 patients in the early phase of acute myocardial infarction and in 306 patients suffering from diseases usually considered in the differen-

tial diagnosis of this condition. An early eosinopenia was found in the great majority of patients with myocardial infarction. Of the counts made on the first, second and third days only 3%, 6% and 15% respectively were above 50 per mm.^{3}. It is concluded that the finding of a normal eosinophil count in the period from 5 to 48 hours following an attack, suspected to be acute myocardial infarction, very strongly contradicts the diagnosis.

An early eosinopenia was found very often in pneumonia, pulmonary embolism, cardiac arrhythmias, acute congestive failure and gallbladder disease, while uncomplicated angina pectoris usually did not reveal significant eosinopenia. Thus the eosinopenia is of no value in the differential diagnosis of myocardial infarction as regards diseases involving severe stress, but may be of some aid as regards uncomplicated angina pectoris.

In 81 patients with eosinopenia of less than 7 days' duration, only 2 patients died. In 23 patients with prolonged eosinopenia 16 patients died. Thus prolonged eosinopenia denotes a poor prognosis.

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SUMMARIO IN INTERLINGUA

Le Signification Diagnostic e Prognostic de Eosinopenia in Acute Infarcimento Myocardial

Contos eosinophilic esseva executate in 149 patientes in le prime phase de acute infarcimento myocardial e in 306 patientes qui suffreva de morbos que es usualmente prendite in consideration in le diagnose differential de acute infarcimento myocardial. Un precoce eosinopenia esseva trovate in le grande majoritate del patientes con infarcimento myocardial. Inter le contos executate le prime, le secunde, e le tertie die, solmente 3 pro cento, 6 pro cento, e 15 pro cento (respectivemente) attingeva valores supra 50 per mm^3. Nos conclude que un normal conto eosinophilic obtenite inter 5 e 48 horas post un attacco que es suspicionate de representar acute infarcimento myocardial es un forte indicio contra ille diagnose.

Precoce eosinopenia esseva trovate multo frequentemente in casos de pneumonia, embolismo pulmonar, arrhythmias cardiac, acute disfallimento congestive, e morbo de vesica biliari. Del altere latere, non-complicate angina de pectore

revelava usualmente nulle significative grado de eosinopenia. Assi, eosinopenia ha nulle valor in le diagnose differential de infarcimento myocardial contra morbos connectite con sever formas de stress; illo pote esser de un certe adjuta in differentiar infarcimento myocardial e non-complicate angina de pectore.

Inter 81 patientes con eosinopenia de minus que 7 dies de duration, il habeva solmente 2 mortes. Inter 23 patientes con prolongate eosinopenia, il habeva 16 mortes. Assi, eosinopenia prolongate es de mal augurio prognostic.

SUMMARIO IN INTERLINGUA

(See page 30 for original article)

Le Tractate Lesion Pulmonar e su Bacillo de Tuberculose
II. Morte e Resurrection

1. Le presente studio concerne le investigation pathologic e bacteriologic de histos pulmonar obtenite per ablation chirurgic in le tractamento de tuberculose. Esseva trovate 48 cavitates aperte, 26 cavitates claudite, 17 cavitates de stadio terminal, e altere lesiones. Le numero del patientes involvite esseva 84. Omnes habeva habite combinate chimotherapias de varie durationes.

2. Inter le 48 cavitates aperte, 44 (92 pro cento) produceva culturas positive que cresceva in 8 septimanas. Un cultura requireva 3 menses. In general, le culturas esseva resistente al un o al altere del major drogas.

3. Ab le 22 cavitates claudite nulle culturas bacillari cresceva intra le usual periodo de 8 septimanas. In 9 casos (41 pro cento) culturas cresceva post periodos de incubation prolongate a inter 3 e 10 menses.

4. Ab le 17 cavitates de stadio terminal, bacillos esseva trovate microscopicamente in 9 casos, sed nulles cresceva in culturas, non mesmo post incubation prolongate.

Iste datos bacteriologic, insimul con le datos pathologic presentate in section I de iste studio, demonstra le obviation de bacillos de tuberculose in certe lesiones. Isto permitte le production del cavitate de stadio terminal per le normal mechanismos del corpore e su stato physicochimic.

Le claudite cavitate con su bacillos in hibernation es apparentemente le resultato de normal mechanismos corporee; in illo il ha pauc manifestationes de effectos drogal. Il esseva in iste typo de lesion que incubationes prolongate demonstrava lor plus grande valor per augmentar le propagabilitate de bacillos latente.

Un alte procentage del classic cavitates aperte revelava rapide crescentias; le bacillos obtenite esseva generalmente resistente a drogas. In le presentia de tal cavitates on debe parlar de "fallimentos chimotherapeutic" quanto al cavitates e a lor bacillos.

Iste remarcas indica eloquentemente que le complete historia es non ancora cognoscite, e si appropriate enzymas (Pope[13]) o altere meliorationes technic es introducite, un plus grande numero de iste bacillos "morte" va possibilemente demonstrar lor vitalitate. Un typo de lesion, illo del cavitates claudite, ha revelate vitalitate bacillari ubi le facto del viabilitate esseva dubitose. Il es ben possibile que altere tal casos existe que es ancora incognoscite. Il ha ancora bacillos que pote esser vidite ben que non culturate per iste technicas. Que va devenir de illos in le corpore? Va modificate conditiones ambiental resurger los? Que es le destino futur de iste adaptate bacillos tuberculotic?

THE COUGH RESPONSE OF NORMAL HUMAN SUBJECTS STIMULATED EXPERIMENTALLY BY CITRIC ACID AEROSOL: ALTERATIONS PRODUCED BY ANTITUSSIVE AGENTS

PART I: METHOLOGY*

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QUALITATIVE comparisons of the relative merit of various antitussive agents were reported in a previous study[1]. Since the assessment was based on the effect of these agents on decreasing the number of coughs produced by stimulating the cough reflex of experimental subjects with citric acid aerosols, it was pointed out that the elicited cough response should have the following characteristics: "1) that the test subject have a uniform response to a given threshold of stimulating agent, 2) that the same individual show reproducibility during the course of the study, and 3) that the method for eliciting cough should be nontoxic and relatively simple in performance in order that studies can be carried out on a large number of subjects."

In this extension of the study, methods were devised for quantitating in healthy subjects, the cough response caused by the inhalation of a standard dose of citric acid. The present report discusses the method of eliciting and recording the experimentally induced coughs. It also analyses the air-flow dynamics of the various cough patterns obtained on 15 healthy subjects tested at repeated intervals for a period of 4 months. The effect of antitussive agents on these cough patterns using a "double-blindfold" technique will be presented in a later report.

Methods. 1. APPARATUS. An open circuit system was devised which consisted of a) an inspiratory loop containing a 9-liter Collins ventilometer connected to a 4-way valve which permitted the shunting of inspired air from the main channel to an aerosol channel of 200 ml. capacity, and b) an expiratory loop containing a lateral pressure tap fitted with an Altec condenser microphone and a pneumotachograph. Unidirectional flow was

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obtained with high speed Sadd valves. A line drawing of the apparatus is presented in Fig. 1.

A 25% aqueous solution of citric acid was nebulized in a glass Vaponefrin nebulizer by oxygen delivered from a high pressure cylinder at 5 L. flow per minute. This produced a stable mist with a mean particle size of 2.5 microns in radius which saturated the aerosol channel. The quantity of citric acid present in the aerosol channel was determined by stoechiometric titration and amounted to 0.045 ± 0.002 mg. citric acid in 200 ml. of air.

microphone and the lower channel recording the air flow in liters per second by means of a pneumotachograph-strain gauge transducer system. In addition to measuring the peak air flows, integration of the area under the curve indicates the total volume of air expelled with each cough.

Before screening tests on experimental subjects could be performed, the various recording instruments were calibrated against a water manometer-pressure transducer system and the total resistance to air flow of the expiratory circuit was determined. In general, the resistance was quite low and offered no

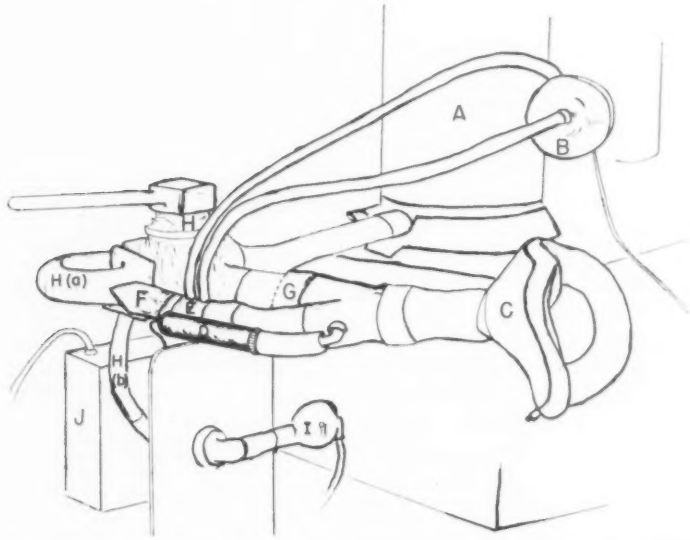

Fig. 1.—Line drawing illustrating the various components of the apparatus. *A*—Ventilometer; *B*—Strain gauge; *C*—Face mask; *D*—Condenser microphone; *E*—Pneumotachograph; *F*—Expiratory flutter valve; *G*—Inspiratory Sadd valve; *H*—4-way valve (*a*) main circuit, (*b*) aerosol circuit; *I*—Nebulizer; *J*—Microphone amplifier.

2. PROCEDURE. The Bennett mask is fitted securely to the subject's face and several resting tidal volumes are recorded by the ventilometer. At the beginning of an expiration the 4-way valve is turned permitting the aerosol channel to be charged with the irritant mist. Kymographic tracings of the following inspiration containing 0.045 mg. of citric acid aerosol record the volume of gas inhaled and the duration of inspiration. The experimentally induced cough is recorded by a twin channel Viso-recorder with the upper channel registering the lateral "sound-pressure" wave in cm. H_2O pressure produced by a displacement in the diaphragm of the condenser

impedance to cough. For the lower flow rates up to 100 L. per minute, the pressure gradient required for 1 L. per minute flow was less than 0.015 cm. H_2O. Over 90% of the total resistance occurred at the pneumotachograph.

3. PILOT STUDIES. A total of 15 healthy subjects consisting of technicians, medical students and research fellows, 5 of whom had participated in our initial experiment, were recruited for this study. There were 6 females and 9 males with a mean age of 31 years. No subject was selected who had a history of a recent upper respiratory infection or evidence of throat irritation. Each individual received a screening test with citric

acid aerosol either preceded by or followed by two additional tests with a distilled water and a normal saline aerosol. If cough was elicited by either of these control aerosols, the subject was omitted from this study.

Each subject was given 3 inhalations of 25% citric acid aerosol with a rest period of 2 to 3 minutes between each inhalation. This constituted a trial and an average of 9 trials were performed on each subject at approximately weekly intervals. These trials were divided equally between morning and afternoon sessions. Notes were kept as to the amount of food consumed prior to testing. Subjects were cautioned against taking any drug with known or suspected antitussive activity on the day preceding the trial. In addition, a "dry run" consisting of a control trial followed by 4 trials at hourly intervals was performed on 9 of the subjects in order to simulate the procedure to be followed in the antitussive study.

Results. In the initial screening tests, it was observed that over 90% (33 of the 35 subjects), selected at random coughed when exposed to the 25% citric acid aerosol and did not respond to distilled water or saline aerosols. The 15 subjects reported in this study were chosen because of their availability and represented a fair sample of this group.

All of the subjects inhaled the same dose of irritant, 0.045 mg. citric acid, at each test. This amount was diluted by the inspiratory tidal volume which ranged between 300 and 600 ml. for the group as a whole. Although considerable variations in the tidal volume were encountered in the same individual on repeated tests, the inspiratory time during which aerosol was inhaled appeared to be much more constant. This is illustrated in Table 1. There was no correlation between the duration of inspiration of the aerosol and the volume of air inhaled.

As noted in the original study, adaptation or a "learning" factor was present in the majority of those subjects not previously exposed to the irritant aerosol. The initial trial usually provoked the greatest number of coughs but after the first 8 inhalations of citric acid, the cough response tended to remain uniform with succeeding tests. Figure 2 shows the mean number of coughs elicited by each of the first 20 inhalations of citric acid in 4 new subjects. Figure 3 is a similar graph representing the frequency response in 3 subjects who participated in previous studies.

In evaluating the reproducibility of the cough response to inhaled citric

TABLE 1.—THE MEAN INSPIRATORY TIDAL VOLUME* AND TIME OF INSPIRATION IN 15 NORMAL SUBJECTS

Subject	*Number of Tests*	*Tidal Volume (ml.)*		*Inspiration Time (seconds)*	
		Mean	*S.D.*	*Mean*	*S.D.*
1. B.C.	28	428	99	0.7	0.1
2. F.G.	28	245	73	1.2	0.3
3. H.B.	31	527	104	0.7	0.1
4. B.Ca.	27	468	121	0.8	0.2
5. H.C.	24	468	166	1.0	0.3
6. S.I.	33	437	141	0.7	0.3
7. E.H.	24	431	95	1.1	0.2
8. H.L.	30	634	244	0.8	0.3
9. J.B.	27	382	67	0.9	0.2
10. J.R.	15	564	142	0.7	0.1
11. F.D.	15	571	153	1.1	0.3
12. E.G.	18	371	31	0.8	0.2
13. B.B.	18	429	95	0.9	0.1
14. D.R.	18	542	94	1.2	0.2
15. J.Bl.	23	384	71	0.9	0.4

* Each tidal volume contains 0.045 mg. citric acid aerosol.

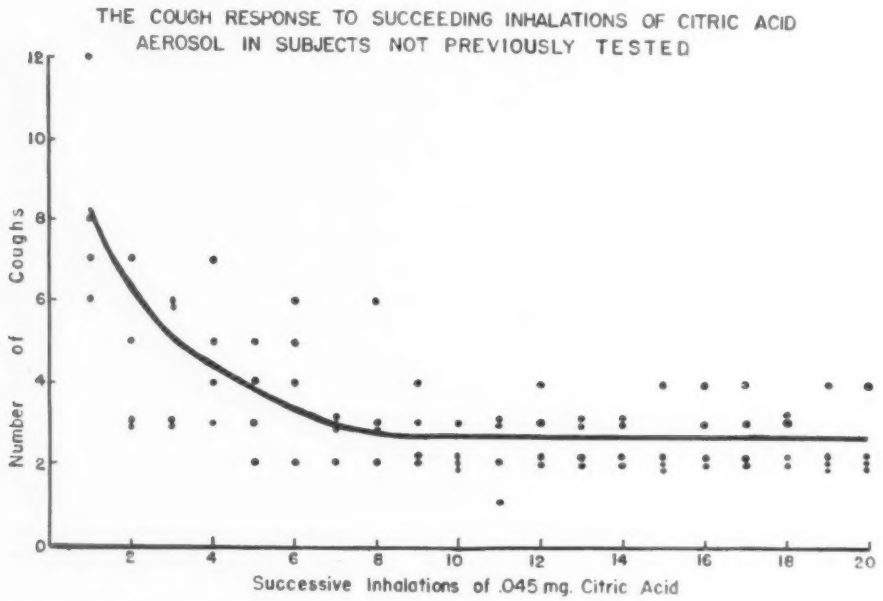

Fig. 2.—The initial slope of this curve illustrates the "learning" factor present in 4 untrained subjects. Stabilization of response occurred after the 7th test.

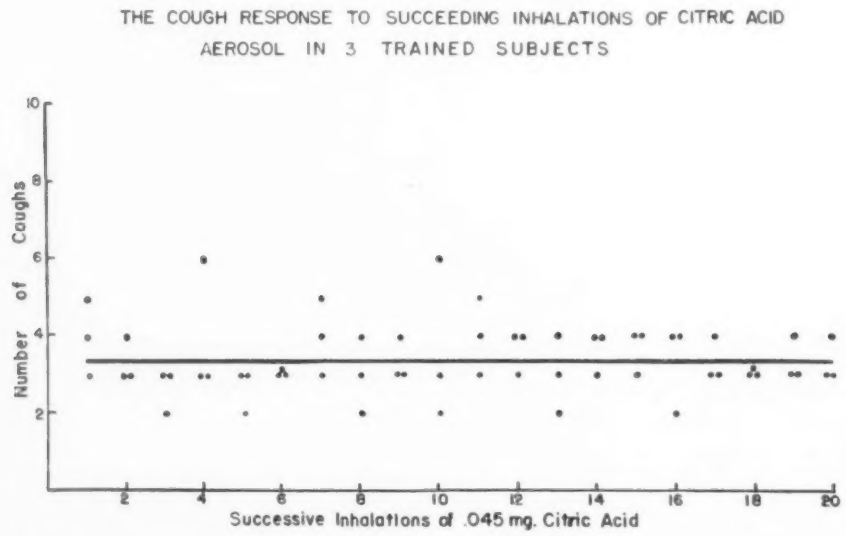

Fig. 3.—The consistency of response as measured by the number of coughs produced by each inhalation is illustrated in these trained subjects.

acid, the first two trials representing the "learning" portions of the curve were discarded in those individuals not previously tested. The mean data obtained on the 15 subjects in terms of number of coughs (frequency), peak flow rates, volumes of air expelled, and the lateral "sound-pressures" are illustrated in Table 2. The subjects were arbitrarily grouped according to their frequency response (mean number of coughs elicited per test): Group A representing 1 to 3 coughs; Group B, 3 to 5 coughs; and Group C, 5 to 7 coughs. Group A with the lowest frequency response showed the greatest variation in the number of coughs with a standard deviation equivalent to 33% of the mean. The standard deviations in Groups B and C represented 21% of the mean. Analyses of the "lateral sound" pressures showed deviations from the means in the three groups identical to the frequency response. The peak air flows showed the highest consistency, with a standard deviation of 15% from the mean in each group. The volume of air expelled varied more than any other response measured, showing deviations from the means of the 3 groups ranging between 34 to 52%. Absence of any correlation between the four characteristics of the cough response measured in this study is illustrated by Table 3 which shows the individual data on 4 subjects with approximately the same frequency response (Group B). Examples of recordings of the lateral "sound pressure" and the air flow on one subject are illustrated in Fig. 4. This subject was given three tests on 3 different days. Consistency of response is indicated by the similarities in number of coughs and configuration of the cough tracings.

Prior to administering the antitussive agents, 9 subjects in this group were tested with 3 inhalations of 0.045 mg. citric acid aerosol at hourly intervals for 4 hours following a control study to simulate the procedure to be followed in assessing the various drugs.

TABLE 2.—VARIATIONS IN THE COUGH RESPONSE OF 15 NORMAL SUBJECTS GIVEN A TOTAL OF 359 INHALATIONS OF CITRIC ACID AEROSOL

			Number of Coughs		*Peak Air Flow (L./sec.)*		*Volume Expelled (ml.)*		*Lat. Pressure (cm. H_2O)*	
*Group**	*No. of Subject*	*No. of Tests*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*
A	5	130	2.4	0.8	3.77	0.57	460	153	7.8	2.4
B	6	139	3.6	0.9	2.42	0.40	143	75	4.3	1.0
C	4	90	6.0	1.3	3.16	0.48	266	85	6.5	1.5

* Cough frequency range per test: A = 1 to 3 coughs
B = 3 to 5 coughs
C = 5 to 7 coughs

TABLE 3.—INDIVIDUAL COUGH RESPONSES OF 4 SUBJECTS WITH THE SAME FREQUENCY RANGE (GROUP B)

		Number of Coughs		*Peak Air Flow (L./sec.)*		*Volume Expelled (ml.)*		*Lat. Pressure (cm. H_2O)*	
Subject	*No. of Tests*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*
B.B.	18	3.3	0.7	3.27	0.43	361	62	4.7	1.4
F.G.	28	3.4	0.9	2.05	0.46	120	61	3.9	0.9
J.B.	27	3.4	1.0	1.72	0.35	128	60	2.9	0.8
E.G.	18	3.9	1.0	2.02	0.34	137	73	2.8	0.7

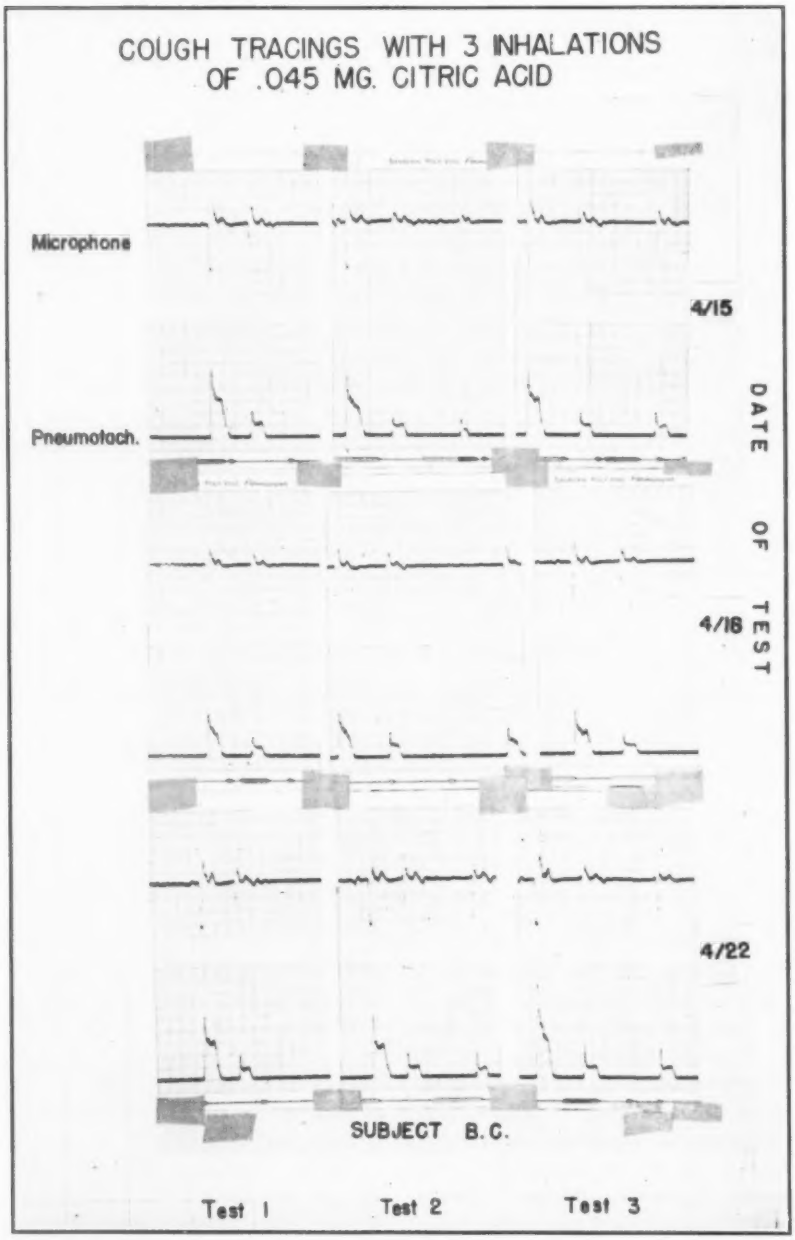

Fig. 4.—Examples of actual recordings showing the lateral "sound pressure" picked up by the microphone and the air flow tracings of the pneumotachograph. Consistency of response is indicated by the similarities in the configuration and number of curves.

The inspiratory time and tidal volumes remained fairly constant in the same individual at each hourly testing period. The mean cough response of each subject showed considerable uniformity throughout the 4-hour period. Combined means of the number of coughs, peak flow rates, volumes expelled and "sound pressures" for the 9 subjects were plotted graphically for each hourly period and is presented in Fig. 5. Each point on these curves represents a mean of 27 tests and the straight-line characteristics of the curves illustrate the consistency of the cough response in the 9 subjects tested.

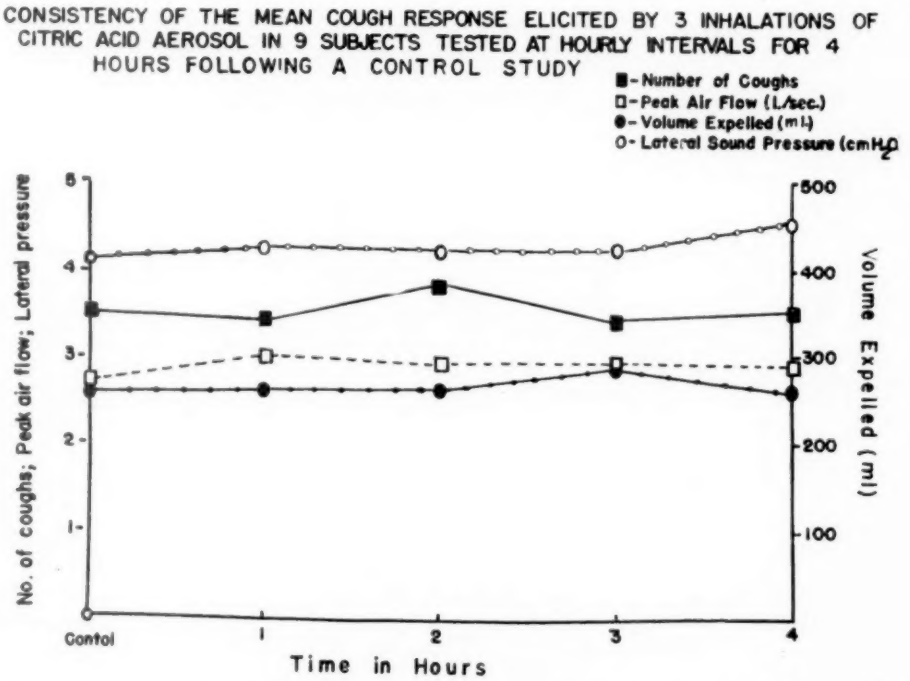
CONSISTENCY OF THE MEAN COUGH RESPONSE ELICITED BY 3 INHALATIONS OF CITRIC ACID AEROSOL IN 9 SUBJECTS TESTED AT HOURLY INTERVALS FOR 4 HOURS FOLLOWING A CONTROL STUDY
■- Number of Coughs
□- Peak Air Flow (L/sec.)
●- Volume Expelled (ml)
○- Lateral Sound Pressure (cmH2O
No. of coughs; Peak air flow; Lateral pressure
Volume Expelled (ml)
Control
1
2
3
4
Time in Hours

Fig. 5.—Combined means of 27 tests performed on each of 9 subjects tested after a 4-hour period illustrates the consistency of the cough response.

Discussion. In a previously reported study[1], it was impossible to provide a fixed amount of citric acid as the cough stimulant. Although the concentration of citric acid could be varied, the quantity inhaled depended upon other factors which could not be controlled, such as 1) the inspiratory tidal volume 2) the duration of inhalation and 3) the loss of aerosol as it was emitted from the nebulizer. In the present investigation, the dosage of aerosol administered can be measured accurately and a constant stimulus provided for each test. This was accomplished by the use of a reservoir saturated with aerosol placed between the ventilometer and the mask. An inspiratory tidal volume in excess of 200 ml. delivers the dose of aerosol when the reservoir system is shunted into the main circuit.

The evaluation of an antitussive agent required more precise data con-

cerning the cough response. In addition to a decrease in the number of coughs, information concerning the effort or "work" of coughing was of considerable importance. The flow rates of air expelled during coughing are related to the intrapulmonary ambient air pressure gradient and inversely proportional to the resistance of the pulmonary system. By recording the peak flow rates and the volume of gas expelled, a relative measure of the intencondenser microphone produced by the cough. The microphone was positioned so that the air stream produced by the cough could not impinge on the diaphragm and thus distort the sound "pick up."

In the present study, a 25% citric acid solution was selected as the irritant aerosol since it appeared to stimulate a moderate response in the majority of the subjects tested. Uniformity of response to repeated stimuli appear-

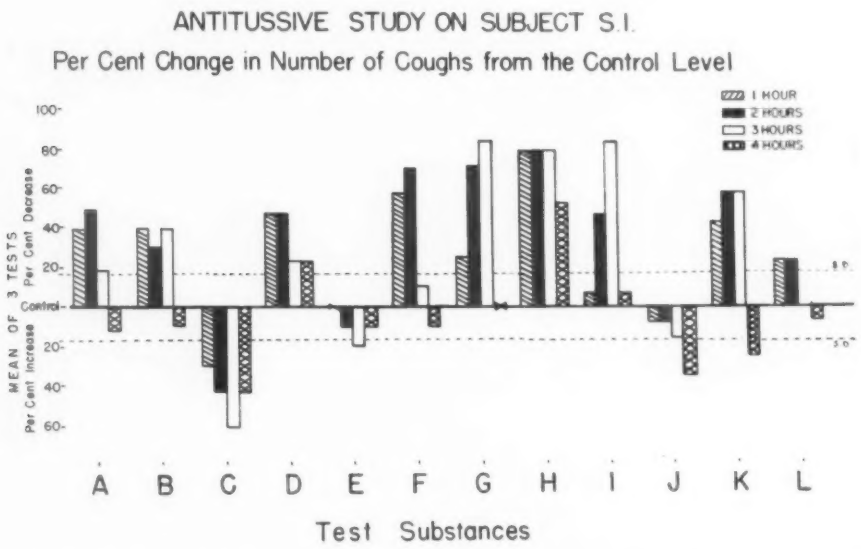

Fig. 6.—Graph illustrating the per cent change in the number of coughs from the control level produced by various test substances in Subject S.I.

sity of the cough could be obtained. Other characteristics of the cough which are capable of assessment are the sound energy level (decibel) and the sound frequency range. The bulky and complicated electronic equipment required to measure these qualities of the cough could not be readily adapted to the apparatus described above. However, a factor related to the sound energy was obtained by recording the displacement of the diaphragm of a

ed to be of the same degree for frequency, peak flow rates and lateral "sound pressures" with greater variations occurring in the volumes of air expelled with each cough. Since good reproducibility was present in the "dry run" study, it was decided to make the initial antitussive evaluation against the cough responses elicited by 25% citric acid aerosol. An illustration of the per cent change in the number of coughs from the control level following

the administration of various "unknown" drugs is presented in Fig. 6. Comment would be premature since this graph represents data on only one subject (S.I.) given a single trial with each drug, in which only one variable, the number of coughs, has been plotted.

Ideally, a potent antitussive agent will produce complete cough suppression with little or no adverse side effects. In practice, however, many of these drugs, in addition to producing varying degrees of cough inhibition, modify the characteristics of the cough by decreasing the intensity or by converting a harsh unproductive cough into a softer and looser one which is less exhausting to the patient. This study will provide an opportunity to observe any significant dissociation between the various factors of the cough response following the administration of antitussive agents. More precise evaluation of these drugs will be obtained by lowering the dose of inhaled irritant to a threshold stimulus level so that cough suppression with active agents becomes complete. From previous studies, it is evident that this threshold stimulus will vary from subject to subject.

Summary. A method has been devised for recording the cough response of human subjects, in terms of the number of coughs, peak air flows, volumes of air expelled, and the lateral "sound pressures," stimulated by a standard dose of citric acid aerosol.

The response to the inhalation of 0.045 mg. citric acid aerosol was measured in 15 normal subjects given a total of 359 tests with the following results:

1) Untrained subjects showed a distinct "learning" tendency with the cough response, becoming more consistent after the first 8 inhalations.

2) Analyses of the mean number of coughs, peak air flows, and the lateral "sound pressures" in trained subjects showed standard deviations varying between 15 and 21% of the means. The volume of air expelled with each cough had the greatest variability.

3) Good reproducibility of the cough response to successive inhalations of citric acid was obtained in 9 subjects retested at hourly intervals over a 4-hour period following a control study.

The testing of antitussive agents by this method is in progress. Adjustment of the dose of citric acid aerosol to a threshold level will make possible more precise evaluations of these drugs.

REFERENCE

1. **Bickerman,, H. A., and Barach, A. L.:** Am. J. Med. Sci., **228**, 156, 1954.

SUMMARIO IN INTERLINGUA

Le Responsa Tussive Stimulate Experimentalmente in Subjectos Human per Aerosol a Acido Citric: Alterationes Producite per Agentes Antitussive Parte I: Methodologia

Esseva disveloppate un methodo pro le registration del responsa tussive de subjectos human, in tanto que illo se manifesta in le numero del tusses, le maximo del fluxo aeree, le volumine del aere expellite, e le lateral "pression acustic," stimulate per un dosage standard de aerosol a acido citric.

Le responsa al inhalation de 0,045 mg de acido citric per aerosol esseva mesurate in 15 normal subjectos, forniente un total de 359 tests con le sequente resultatos.

1. Subjectos novicios monstrava un distincte tendentia a "apprender" in le curso del responsas tussive, le quales deveniva plus constante post le prime 8 inhalationes.

2. Le analyse del numeros median de tusses, del maximos de fluxo aeree, e del lateral "pressiones acustic" in subjectos experientiate monstrava deviationes standard de inter 15 e 21 pro cento del valores median. Le volumine del aeree expellite con le tusses individual monstrava le plus grande variabilitate.

3. Le reproducibilitate del responsas tussive al inhalation de acido citric esseva bon in 9 subjectos in qui le test esseva repetite a intervallos de un hora durante un periodo de 4 horas precedite per un studio de controlo.

Le evalutation de agentes antitussive per iste methodo es in progresso. Le adjustation del dose de aerosol a acido citric a un nivello liminal va render possibile un plus exacte evalutation de iste drogas.

SUMMARIO IN INTERLINGUA

(See page 8 for original article)

Quantitation del Activitate de Arthritis Rheumatoide 2. Recession del Rigor Matinal in Patientes Progredente Verso Remission

1. Rigor matinal es un manifestation quasi universal de active arthritis rheumatoide.

2. Le majoritate del patientes es capace a observar accuratemente le duration de rigor matinal.

3. Le duration del rigor matinal es grossiermente correlationate con le maximos de sedimentation erythrocytic pro periodos de 5 minutas (secundo Cutler) sed pare non esser relationate a etate, sexo, duration del morbo, e concentration hemoglobinic.

4. Es presentate tres analyses graphic. Illos indica que le duration del rigor matinal tende a reducer se regularmente in tanto que le patiente progrede verso remission.

5. Le duration del rigor matinal es consequentemente valide como indice del componente general o fibrositic del activitate rheumatoide e merita esser includite routinarimente in le protocollo de progresso.

AN EVALUATION OF THE SINGLE BREATH TECHNIQUE FOR MEASURING ANATOMIC RESPIRATORY DEAD SPACE WITH THE NITROGEN METER*

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A thorough evaluation of the physiologic function of the lungs in normal persons and in patients with pulmonary disease includes a study of the volume of anatomic and physiologic dead space. In the past, the methods employed for measuring anatomic and physiologic dead space were either too complicated for routine use or did not yield dependable and reproducible values. In the resting state in normal persons, the values obtained for anatomic and physiologic dead space were variable but reproducible within a narrow range. However, during exercise and in patients with uneven alveolar ventilation the variation of the values obtained was accentuated because of increased errors in alveolar gas sampling techniques. The variant results obtained by Krögh and Lindhard[8] and Douglas and Haldane[4] illustrate the difficulties of obtaining accurate values for the anatomic and physiologic dead spaces, dependent upon intermittent alveolar gas sampling. With the advent of the nitrogen meter, it was possible to analyze continuously expired gas and a method was devised by Fowler[5,6,7] for calculating respiratory dead space. He[5] originally defined the dead space measured with the nitrogen meter as physiologic. Comroe[3] defines the dead space measured with the nitrogen meter as anatomic.

In this manuscript we, as Comroe[3], define anatomic respiratory dead space as the volume of the conducting airway from the nose and mouth down to the alveoli. In this dead space there is no significant exchange of oxygen and carbon dioxide between the gas and blood during respiration. As outlined by Comroe[3], physiologic dead space includes the anatomic dead space and the volume of inspired gas ventilating alveoli with no pulmonary capillary blood flow or the volume of in-

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**Mathematical consultant, Department of Physiology, University of Minnesota and Veterans Administration Hospital, McKinney, Texas.

spired gas ventilating alveoli in excess of that required to oxygenate the pulmonary capillary blood perfusing them, or both.

In this paper the respiratory dead spaces evaluated are anatomic. It includes an evaluation of the single breath nitrogen meter method of measuring anatomic dead space. The fundamental principle involved in using the nitrogen meter for measuring anatomic dead space is that formulated by Bohr[2]. It is our purpose to report a method of measuring anatomic dead space with the single breath technique using the nitrogen meter different from that in current use which can become a reliable test in any laboratory in which the proper equipment is available.

In attempting to obtain reproducible values for anatomic dead space in normal individuals and patients having pulmonary disease with methods of analyses of the curves obtained with the nitrogen meter single breath technique in current use[5], it was found with our equipment and technique that the method did not in our hands have the accuracy desired in normal persons and in patients with pulmonary disease in which there was modification of pulmonary elastance, increased uneven alveolar ventilation, and obstruction of the respiratory airways. This was especially true in patients with pulmonary emphysema when the nitrogen meter curve had no plateau at the end of expiration. A different and simpler method was evolved for treating the curves to obtain dead space values. This method was found to corroborate the results calculated with the Bohr mathematical principle and a dead space model with known dead space values.

Method. A. INSTRUMENTATION. A Waters Conley nitrogen meter was used to study the changing concentration of nitrogen in a single breath during expiration. The output of the nitrogen meter was led into a 12-channel Electronics for Medicine Physiologic Recorder. There was a latency interval of 0.2 second between the nitrogen meter and pneumotachograph response because of the time required for the gas to traverse the sampling tube to the analyzer. Volume-flow measurements were made with a pneumotachograph, which was calibrated daily with air. There was no significant difference between the oxygen and air calibration factors. The differences in response time of the pneumotachograph and the nitrogen meter were carefully measured from time to time.

B. SUBJECTS. The age range, body surface, and number of normal persons in each group studied are listed in Table 3.

C. PROCEDURE. The normal subjects sat in a chair, breathing room air through a mouthpiece for several minutes. The system of valves was perfused with oxygen to remove all nitrogen. At the termination of a normal expiration, a valve was turned and the subject inspired 100% oxygen. Upon completion of a maximal inspiration, the subject expired slowly and uniformly the gases from the lungs. The breath-holding period at the termination of the maximal inspiration was less than one second. The pneumotachographic and nitrogen meter curves were analyzed in the same way as the model dead space curves shown in Figs. 2 and 3. The method of analysis of the nitrogen meter curves described in this report is designated as method A. The problem which presents itself in the analysis of the nitrogen meter curve is to locate the proper point on the curve to project upon the pneumotachographic curve in order to calculate the volume of the anatomic dead space. This point is described as the *inflection point* of the nitrogen meter curve. It is here that the slope of the nitrogen meter curve is equal to zero, because the rate of change of nitrogen concentration in the anatomic dead space passes from increasing to decreasing values when the alveolar gases have washed the anatomic dead space free of oxygen inhaled during the initial maximal inspiration at the beginning of the test.

If one takes the first derivative of the nitrogen meter curve with respect to time and plots it as shown in Fig. 1, it can readily be seen that at the inflection point, the slope of the curve changes from increasing to decreasing values. In order to locate the inflection point precisely, one takes the second derivative of the nitrogen meter curve with respect to time, or the derivative of the first derivative and plots it so that where the curve

crosses the zero line, the inflection point is established. If one corrects for the lag time between the pneumotachograph and the nitrogen meter curve, and projects the inflection point onto the volume flow curve of the pneumotachograph, he may then calculate accurately the volume of the anatomic dead space of either a model or a patient. These geometrical and mathematical performances are complicated and time-consuming. Therefore, a simpler method was designed as reported in this publication. The performance of the new method of analysis is the following: a fine line was superimposed on the steepest and straightest portion of the nitrogen meter curve. At the upper and lower ex-

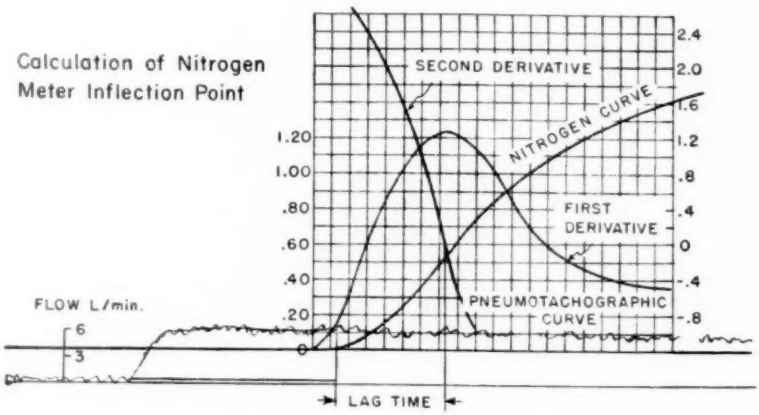

Fig. 1.—The method of locating the inflection point of the nitrogen meter curve by taking and plotting the first and second derivatives. The scale on the left is for the first derivative slope values. The one on the right is for the second derivative.

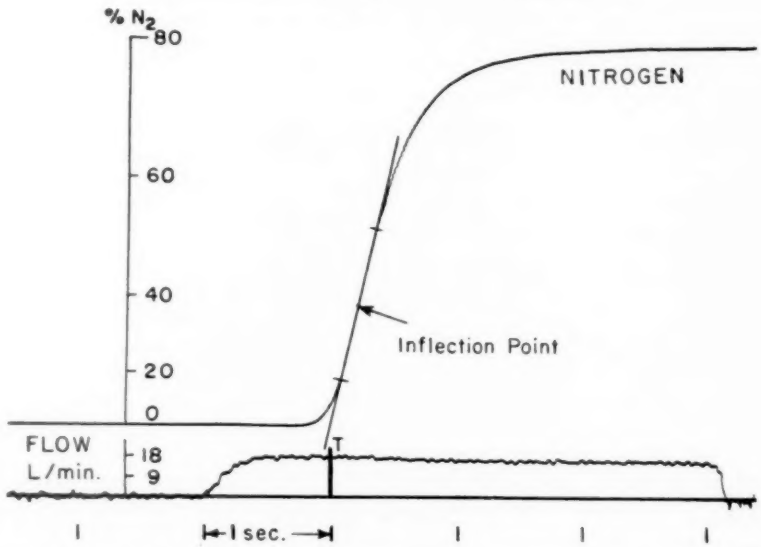

Fig. 2.—A photograph of a nitrogen meter model dead space curve showing the simple method of geometric analysis. The upper portion is the nitrogen meter curve and the lower, the pneumotachographic curve. The inflection point on the nitrogen meter curve minus the time lag was projected on the volume flow curve at line T.

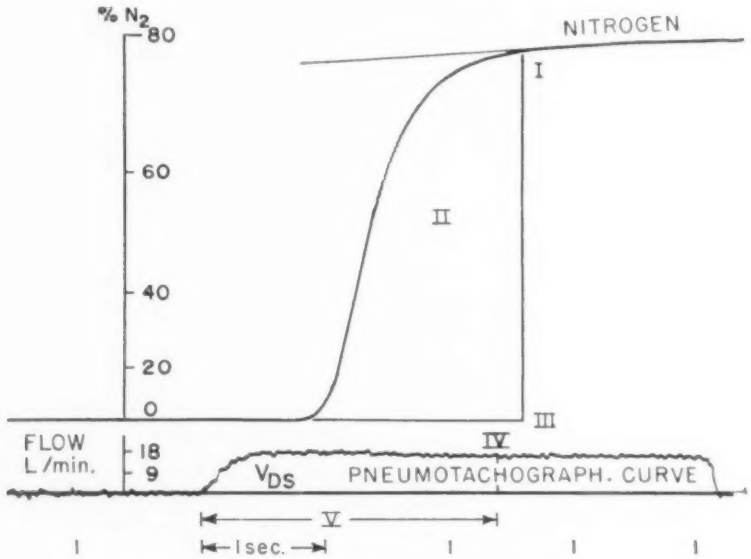

Fig. 3.—A photograph of the same model dead space curve as shown in Fig. 2 to illustrate the Bohr method of calculating dead space:

I = Concentration of nitrogen in the bellows.
II = Mean concentration of nitrogen from the bellows as it flows through the dead space.
III = Concentration of nitrogen in the oxygen of the dead space of the model.
IV = Area under pneumotachographic curve integrated to calculate dead space of the model.
V = Volume of air from the bellows to wash oxygen from the dead space.
V_{DS} = Volume of model dead space.

TABLE 1.—RESPIRATORY ANATOMIC DEAD SPACE CALCULATED WITH THE AUTHORS' METHOD AND COMPARED WITH KNOWN MODEL DEAD SPACE

	Volumes in ml.			
Model No.	*1*	*2*	*3*	*4*
Determination No.				
1	112.4	134.9	176.3	207.3
2	116.0	134.9	186.6	207.3
3	112.4	134.8	171.2	217.8
4	119.4	134.8	176.3	199.2
5	112.5	129.6	171.2	207.3
6	112.5	124.3	176.3	207.3
7	112.5	145.2	171.1	217.8
8	112.5	140.0	176.3	217.7
9	105.4	134.9	165.9	207.3
10	112.5	145.1	176.3	207.4
11	109.2	134.9	166.0	212.5
12	115.9	129.6	165.9	207.4
13	116.0	134.8	176.3	207.3
14	116.0	134.8	176.3	207.4
15	112.7	129.6	171.1	217.7
Mean ± S. D.	113.2±3.3	134.8±5.6	173.5±5.5	209.9±5.5
Actual D. S.	111.0	133.0	171.0	209.0

tremity of the straightest portion of the nitrogen meter curve, where the superimposed line departed from it, a point was placed. One-half of the distance between these two points was found to be the inflection point of the nitrogen meter curve. When this point, less the differences in response time of the nitrogen meter and pneumotachograph, was projected onto the volume flow curve of the pneumotachograph, the volume of the anatomic dead space could be calculated. A planimeter was used to calculate the area under the pneumotachographic curve. In order to substantiate this new method of analysis of the nitrogen meter curve for calculating anatomic respiratory dead space, a model was constructed, consisting of a bellows and a known dead space. The model was constructed so that dead spaces of different volumes could be substituted, one for the other. Known dead spaces having values of 111.00, 133.00, 171.00, and 209.00 ml. were used. Typical curves obtained from the model dead space apparatus are shown in Figs. 2 and 3. The curves obtained from the model dead space studies were subjected to the author's, Bohr's[2], and Fowler's[5] methods of analysis. Fifteen determinations were made with each known dead space volume, as shown in Table 1.

The data were treated with the Bohr formula for calculating anatomic dead space. It is designated as method B (Fig. 3). The formula states that an expired breath consists of a mixture of several parts, each with a different concentration of the respiratory gases: (1) the atmospheric gas in the upper airway compartments of the respiratory system in which there is no oxygen and carbon dioxide exchange with the blood; and (2) the gas in the lower sections of the respiratory airway system containing varying mixtures of alveolar gas and atmospheric air. If one knows the volume of expired air, the concentration of a gas in the expired air, the concentration of the gases in the alveolar air, and the concentration of the gases in the inspired air, one has all the data with which to solve the Bohr equation (Fig. 3).

$$V_e \times C_e = (V_e - V_{ds})\, C_a + V_{ds} \times C_i$$

V_e = Volume of expired air
C_e = Concentration of a gas in V_e
V_{ds} = Volume of dead space
C_a = Concentration of the same gas in alveolar air
C_i = Concentration of same gas in inspired air

All gas volumes were corrected to 760 mm. Hg, 37° C. and 47 mm. Hg water vapor.

The nitrogen meter single breath dead space curves were subjected to a third method of analysis devised by Fowler[5]. In this report it is designated as method F. Essentially, his analysis of the nitrogen meter curves was to substitute for the curve of the meter a vertical line which represented a square front between dead space and alveolar air. He computed the volume of air expired before the front arrived at the nitrogen meter sampling point and obtained the volume of the conducting airway down to the point at which a large change in gas composition occurs.

Anatomic dead space was measured in the sitting and supine positions, during hyperventilation, exercise, maximum expiratory and high inspiratory positions, and with bronchodilators using method A. The breath holding time was less than a second in the study.

Results. Known dead space No. 1, Table 1, having a volume of 111.0 ml., was inserted into the model. The volume of this dead space was obtained 15 times and calculated with method A. The mean value was 113.2 ± 3.3 ml. This procedure was repeated with models No. 2, 3, and 4 having known values of 133.0, 171.0, 209.0 ml. respectively. The mean and standard deviations of these model dead spaces were 134.8 ± 5.6, 173.5 ± 5.5 and 209.9 ± 5.5.

The curves of the first five model dead spaces listed in Table 1 were analyzed further with the methods B and F. The complete comparative data showing the results of different methods of calculating anatomic dead space are listed in Table 2. There was no significant difference between the mean values of methods A and B; however, a significant difference was obtained by calculating the known model dead spaces with method F.

The anatomic dead spaces were obtained in 63 normal persons. The range of the ages and mean dead space values are listed in Table 3. The anatomic dead space increased with age. When the subject changed his position from sitting to lying there was a significant

decrease in the anatomic dead space. Maximal expiration decreased the airway volume and maximal inspiration increased the value. In all age groups, hyperventilation increased the dead space. There was a small but significant increase in the dead space values during exercise. Bronchodilators caused an increase in the volume of the respiratory airways in all age groups studied.

The measurement of anatomic respiratory dead space with the single breath nitrogen curve in patients with severe pulmonary emphysema (Fig. 4) creates additional problems. The curves are extremely unsymmetrical and there is no plateau; therefore, the use of method F is rendered more difficult. The more basic mathematical Bohr method yielded a mean value of 125.2 ml. in 4 determinations. Method A gave a mean value of 128.4 ml. for 4 determinations in a patient with severe pulmonary emphysema. In the few patients with pulmonary emphysema studied to date, the anatomic dead space is diminished and the physiologic dead space is remarkably increased[9].

Discussion. The volume of the anatomic dead space in a given person varies from breath to breath. This has been verified by direct observation during bronchoscopy because one observes the bronchi to expand and contract at intervals, with and independent of respiratory changes in pulmonary volume. The three methods used in this study for calculating dead space yielded data which indicate variation of the volume of the anatomic pulmonary dead space from breath to breath. This variation from breath to breath is not because of gas exchange in the trachea and bronchi because this has been found with simultaneously measured nitrogen, oxygen, and carbon dioxide dead spaces[1]. If there were significant gas exchange in the anatomic dead space, the value for each would be different. Thus there is an absolute dead space increase and decrease concurrent with inflation and deflation of the lungs.

On moving from the sitting to supine position, there is a decrease in the dead space. This was also observed by Fowler[6]. The total pulmonary volume

TABLE 2.—A COMPARISON OF KNOWN MODEL DEAD SPACE

	Calculated with:			
*A—Authors' Method	*B—Bohr Equation		*F—Fowler's Method	
	No. 1	*No. 2*	*No. 3*	*No. 4*
Actual Model Dead Space ml.	111.0	133.0	171.0	209.0
Model Dead Space ml.	112.4	134.9	176.3	207.3
	116.0	134.9	186.6	207.3
Calculated with	112.4	134.8	171.2	217.8
Method A*	119.4	134.8	176.3	199.2
	112.5	129.6	171.2	207.3
Model Dead Space ml.	114.0	123.9	187.3	213.7
	115.8	136.6	175.0	200.4
Calculated with	112.0	143.3	175.8	216.6
Method B*	107.3	135.2	165.1	193.3
	110.2	135.6	181.2	207.9
Model Dead Space ml.	144.0	171.1	223.0	258.6
	144.0	181.4	222.9	331.7
Calculated with	144.2	191.9	217.7	331.7
Method F*	137.0	186.6	233.4	282.9
	137.1	176.2	223.0	330.4

TABLE 3.—THESE DATA REVEAL THE EFFECT OF AGE, POSITION OF THE BODY, DEGREE OF PULMONARY INFLATION, HYPERVENTILATION, EXERCISE, AND BRONCHODILATION ON ANATOMIC RESPIRATORY DEAD SPACE VOLUME IN ML. EACH DEAD SPACE VOLUME IS THE AVERAGE OF THREE MEASUREMENTS.

Group	*No. of Persons in Group*	*Age Range in Years*	*Mean Body Surface Area Sq. M*	*Sitting*	*Supine*	*Maximum Expiration*	*High Insp.*	*Voluntary Hyperventilation*	*Light Exer.*	*Bronchodilator Sitting*
1	33	12–19	1.75	149.5	130.7	140.0	150.7	151.0	158.2	–
2	7	22–28	1.81	154.0	144.5	152.6	164.7	161.2	–	160.3
3	10	33–39	1.86	157.7	144.5	150.5	165.4	166.1	–	166.5
4	5	40–46	1.79	156.6	147.4	142.0	157.0	163.2	–	167.8
5	4	54–59	1.90	161.1	143.3	153.6	161.8	183.6	–	166.2
6	4	60–63	1.95	160.7	151.2	157.5	158.1	195.9	–	172.5

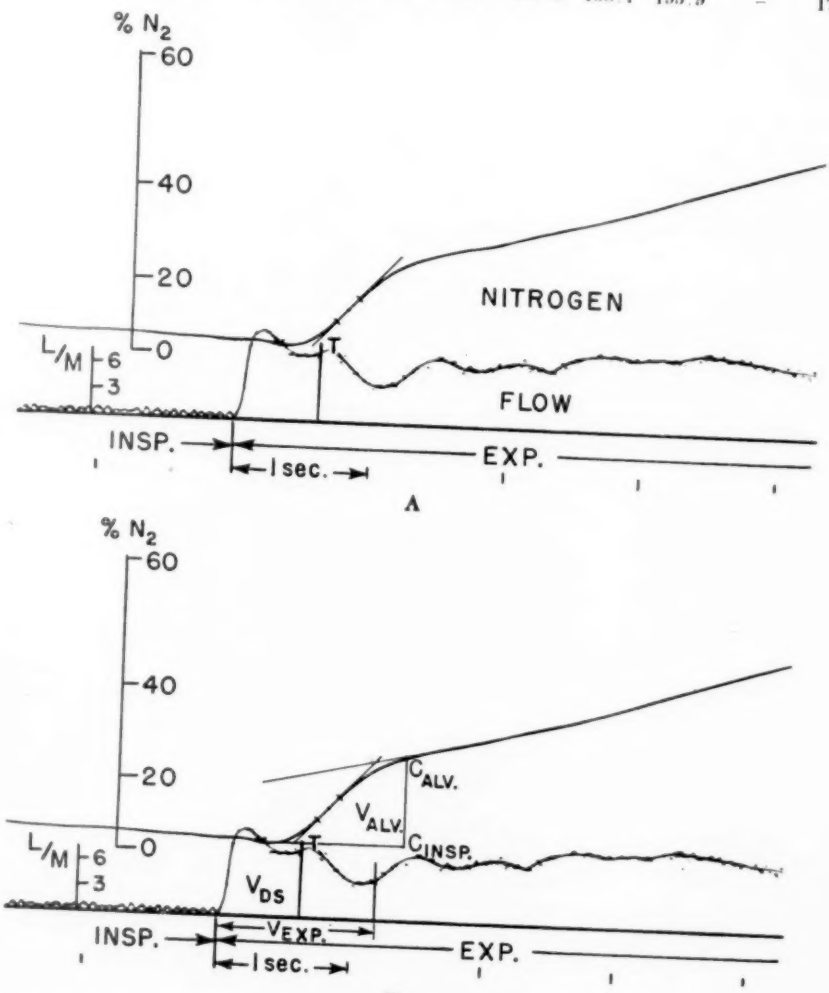

Fig. 4.—A single breath curve from a patient with severe pulmonary emphysema comparing methods A and B for calculating anatomic dead space. The upper portion is the author's method and the lower portion of the figure is an illustration of Bohr's method.

was found to diminish when a subject changed from the sitting to supine position. Since airway diameter and length are related to the state of pulmonary inflation, as a whole, this alteration of anatomic dead space is to be expected on changing from the sitting to the supine position.

Further evidence that changes in the volume of the lung have an effect on the volume of the anatomic dead space is shown in Table 3. There was a consistent decrease in dead space when the lungs of the subject were in the maximal expiratory state. The opposite was found when the dead space was measured when the lungs were expanded during deep breathing.

Voluntary hyperventilation and exercise expand the anatomic dead space. It was observed that inhalation of bronchodilators increased the airway volume in normal persons.

In this discussion we will not attempt to improve upon Fowler's[5] and Comroe's[3] ingenious concepts of the composition of the various gases which flow past the sampling leak of the nitrogen meter during a single breath. The concept of Bohr[2] which has been verified again and again has been found to be infallible in this study. Herein the authors have devised a simpler method of locating, on a single breath curve written by the nitrogen meter, a point representing transition from increase to decrease in the rate of change of nitrogen concentration in the expired air, that is, where the slope of the curve is zero. During the initial phase of expiration while the anatomic dead space is being rendered free of oxygen, there is an increase in the rate of change of nitrogen concentration. As the anatomic dead space is freed of oxygen by the flow of alveolar nitrogen, the rate of increase of the nitrogen concentration in the expired air is diminished in contradistinction to the absolute quantity of nitrogen. Thus this is the point on the nitrogen meter curve to be projected onto the volume-flow curve of the pneumotachograph representing the specific volume of alveolar gas required to remove the oxygen from the anatomic dead space. Since the interface between the gases flowing from the alveoli and dead space is not a square wave the curve is unsymmetrical. The inflection point will alter its position with change in slope of the steepest portion of the curve, and at a level representing the start of decrease in the rate of change of nitrogen concentration flowing past the sampling leak of the nitrogen meter. The symmetry of the nitrogen meter curve is determined by the concentration of oxygen and nitrogen in the expired gas. If the nitrogen meter curve were perfectly symmetrical, methods A, B, and F would yield identical answers. However, such will not be the case in most instances; therefore, methods A and B are preferable to F in calculating anatomic dead space. Further, the method of analysis of the single breath nitrogen meter curves which is presented in this publication is remarkably flexible and can be used for estimating the anatomic dead space in patients with pulmonary diseases which markedly alter the dynamics of gas flow.

The size of the model anatomic dead space calculated with method A compares favorably with the known space and that calculated with the more complicated and lengthy Bohr formula as shown in Table 2.

A few technical expedients were discovered during the course of these experiments: the rate of flow of expired air past the leak of the nitrogen meter must be held within a range which will permit the nitrogen meter to follow accurately the change in concentration of nitrogen in the expired air. Small

irregularities in the volume of gas flow through the pneumotachograph cannot be avoided in persons with severe pulmonary disease. In fact, the lack of uniformity of flow when it is of small magnitude causes an insignificant error in the anatomic dead space calculation. The nitrogen meter sampling tube must be as short as feasible to prevent a lengthy lag between the response of the pneumotachograph and nitrogen meter. The pressure of the nitrogen meter should be rigidly controlled within the optimal operating range which is usually 400 to 600 microns of mercury. If this precaution is not observed, reproducible values for anatomic dead space cannot be obtained from breath to breath.

Summary. A new geometric and mathematical method for estimating anatomic dead space from the nitrogen meter single breath curves has been presented. The new method produces anatomic dead space values equal to those calculated with the Bohr formula and a formula for a model with known dead space values.

Anatomic dead space increases with age. It varies with the change of pulmonary volume during respiration.

Hyperventilation with or without additional exercise leads to an increase in anatomic dead space. It decreases in changing from the sitting to the supine position. In the patients studied with pulmonary emphysema, the anatomic dead space was decreased or was normal and the physiologic dead space was increased.

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SUMMARIO IN INTERLINGUA

Evalutation del Technica a Respiration Unic pro Mesurar le Anatomic Spatio Morte Respiratori per Medio del Nitrogenometro

Es presentate un nove methodo geometrico-mathematic pro estimar anatomic spatio morte ab curvas nitrogenometric a respiration unic. Le nove methodo produce valores de anatomic spatio morte equal al valores calculate per medio del formula de Bohr e un formula pro un modello in que le valores de spatio morte es cognoscite.

Le anatomic spatio morte cresce con le etate del subjecto. Illo varia con le volumine pulmonar durante le respiration.

Hyperventilation con o sin exercitio additional resulta in un augmento del anatomic spatio morte. Iste spatio morte decresce quando le subjecto se move ab un position sedente a un position de decubito dorsal. In patientes con emphysema pulmonar nos trovava que le anatomic spatio morte esseva reducite o normal durante que le physiologic spatio morte esseva augmentate.

APPARENT RENAL DEFECT IN SICKLEMIC INDIVIDUALS*

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Sickle cell anemia was first reported by Herrick[6] in 1910. In addition to describing the principal clinical and hematologic features of his patient, Herrick also recorded the urine specific gravity readings which ranged from 1.010 to 1.014. Mason[12] in 1922, and Huck[7], Sydenstricker[15] and other early students of the disease called attention to the low specific gravity of the urine in their cases. Following these early observations, however, the renal status of sicklemic individuals received little attention for almost a quarter century. Indeed, as late as 1950, Henderson[5], in his excellent review, cited the generally accepted statement that the specific gravity is fixed in sickle cell anemia, and called for further and more detailed renal studies in this group.

Some years ago we became aware of low specific gravity findings in our own cases of the disease and were impressed by the absence of associated clinical signs of renal impairment. The present study was undertaken, therefore, in order to evaluate renal function in sicklemic subjects. Preliminary observations[16,17] provided the discovery that an inability to concentrate urine normally is not only a feature of sickle cell anemia as reported by others (Kunz *et al.*[9]), but is also present in individuals manifesting the trait for sickling[16,17]. Since this finding was present in all 7 cases of sickle cell anemia and all 14 individuals with sickle cell trait tested, it was postulated that the renal defect might be transmitted genetically. In an effort to test this hypothesis further, the studies were extended to additional subjects with sicklemia. The cumulative findings in these investigations form the basis of the present report.

Material and Methods. PATIENT MATERIAL. A total of 52 individuals who exhibited sickling of their erythrocytes in one or more of 4 tests for the phenomenon have so far been studied. On the basis of clinical, hematologic, and electrophoretic evidence there were 16 cases of sickle cell anemia and 33 of sickle cell trait. Two additional patients had sickle cell trait and thalassemia minor, while another manifested both sickle cell trait and hemoglobin C trait.

The patients with sickle cell anemia ranged in age from 15 to 44 years, while the age of the trait subjects varied from 13 to 57 years.

*Aided in part by the Temple University Hematology Research Fund.

Twenty-one of the individuals were males, and 31 were females. Seven of the sickle cell trait group were white (Italian); the remaining subjects were Negroes.

Whenever possible other members of the subjects' families were studied. In this manner, nonsickling and genetic relationships could also be considered. In addition, several subjects with thalassemia trait and other long-standing anemias were also tested.

1.1% saline solutions for intervals up to 24 hours.

Complete urinalyses, 18-hour urine concentration tests, and maximum osmotic pressure of the urine as determined by freezing point depression were performed in all cases. The 18-hour urine concentration test was repeated in several subjects after the intramuscular administration of 5 units of pitressin tannate in oil. Blood urea nitrogen and creatinine deter-

TABLE 1.—RESULTS OF PERTINENT RENAL STUDIES IN 16 CASES OF SICKLE CELL ANEMIA

Test	*No. Cases*	*Range*	*Mean*	*σ*
Maximum urine specific gravity*	16	1.006 to 1.016	1.011	±.0026
Maximum urine osmotic pressure**	14	326 to 551	420.7	±72
Blood urea nitrogen	8	5 to 16 mg.%	8.25 mg.%	±3.4 mg.
Urea clearance (% Normal)	8	60 to 173%	121%	±40.5%
Serum creatinine	10	0.72 to 1.5 mg.%	1.08 mg.%	±0.28 mg.
Creatinine clearance (% Normal)	10	65 to 151%	103%	±28%
Phenolsulfonphthalein excretion, 1 hr. total	11	51 to 87%	67.6%	±11.8%

*After 18 hr. fluid deprivation.
**By freezing point depression, in mOsm. per liter.

TABLE 2.—RESULTS OF PERTINENT RENAL STUDIES IN 36 CASES OF SICKLE CELL TRAIT*

Test	*No. Cases*	*Range*	*Mean*	*σ*
Maximum urine specific gravity**	36	1.010 to 1.029	1.0167	±.0045
Maximum urine osmotic pressure**	36	413 to 980	604	±154
Blood urea nitrogen	24	7 to 18 mg.%	11.85 mg.%	±3.14 mg.
Urea clearance (% Normal)	23	72 to 175%	107%	±28
Serum creatinine	24	0.7 to 1.9 mg.%	1.18 mg.%	±0.37 mg.
Creatinine clearance (% Normal)	23	51% to 150%	98.6%	±24.4%
Phenolsulfonphthalein excretion, 1 hr. total	25	48 to 88%	66.4%	±8.5%

*Including 2 patients with mixed sickle cell trait and thalassemia minor, and 1 patient with sickle cell trait and hemoglobin C trait.
**Key same as for Table 1.

LABORATORY STUDIES. All patients had complete hematologic evaluation with determinations of the hemoglobin, erythrocyte count, and hematocrit; leukocyte count, differential, and erythrocyte morphology; reticulocyte counts; platelet counts; and determination of fetal hemoglobin by the alkali resistance method. Quantitative erythrocyte fragility tests, hemoglobin electrophoresis, and blood group genotyping were performed in many instances. Tests for sickling were carried out using the Diggs method, the sodium metabisulfite technique, and by incubating petrolatum rimmed erythrocyte suspensions in 0.9% saline and minations, Addis counts, urea and endogenous creatinine clearance tests, and phenolsulfonphthalein excretion at 20, 40, and 60 minutes after intravenous dye injection (6 mg.) were done in the majority of subjects, while intravenous pyelography and Hickey-Hare tests were performed in selected cases.

Results. The results of the principal renal function tests used in this study are summarized in Tables 1 and 2. It can readily be seen that the mean values for blood urea nitrogen, urea

clearance, serum creatinine, creatinine clearance, and phenolsulfonphthalein excretion are normal for the sickle cell anemia patients as well as for the sickle cell trait individuals tested. The most striking finding in both groups of subjects was the limited ability to excrete a concentrated urine as determined by specific gravity and osmotic pressure methods. From inspection of the tables it can be seen that this defect was more pronounced in the sickle cell anemia subjects than in the sickle cell trait individuals. In the former group, the mean specific gravity after 18-hour urine concentration tests was 1.011 while the sickle cell trait group was found to have a mean value of 1.017. The mean maximum urine osmotic pressure was 421 mOsm. per liter in the sickle cell anemia subjects and 604 for the sickle cell trait patients.

The type of response obtained in the Hickey-Hare tests in each of 9 subjects tested is shown in Fig. 1. Excellent urine dilution was achieved through hydration. Following the intravenous infusion of 3% NaCl, there was a rapid decrease in urine flow with a rise in specific gravity. The urine concentration was maximal, without further increase upon the intravenous injection of 0.1 unit of pitressin. These findings were interpreted as indicating that the pituitary-osmoreceptor response was normal in this group of patients.

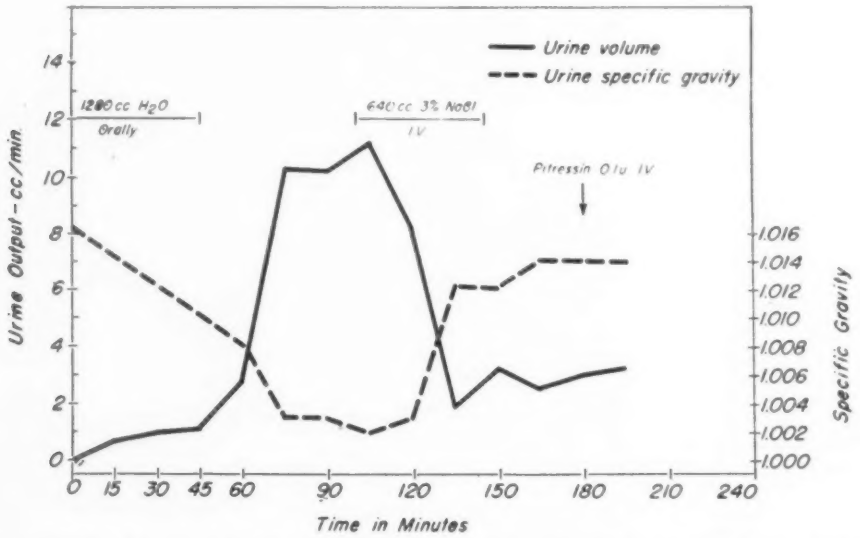

Fig. 1. Hickey-Hare test in 19-year-old patient (R.D.) with sickle cell anemia. Note ability to excrete dilute urine after hydration, limited response to infusion of hypertonic saline, and absence of further concentration of urine after intravenous injection of pitressin.

The members of two families were studied in detail. In Fig. 2, the age and hemoglobin value of each member of the W family is shown along with an indication whether or not they have sickle cell trait or sickle cell anemia. Results of the 18-hour urine concentration tests in members of this family are shown in Fig. 3. It may be noted that the grandfather with 11.4 gm. hemoglobin concentrated to 1.027, and

the eldest son to 1.026. Neither of these individuals have sickle cell hemoglobin by the conventional tests or by paper and Tiselius electrophoresis.°

The findings in the D' family, who are of Italian origin, are given in Fig. 4. Several members of this family exhibit sickle cell trait; others the thalassemic trait, and two appear to have microdrepanocytic disease. Again it may be noted that low specific gravity of the urine was obtained in subjects

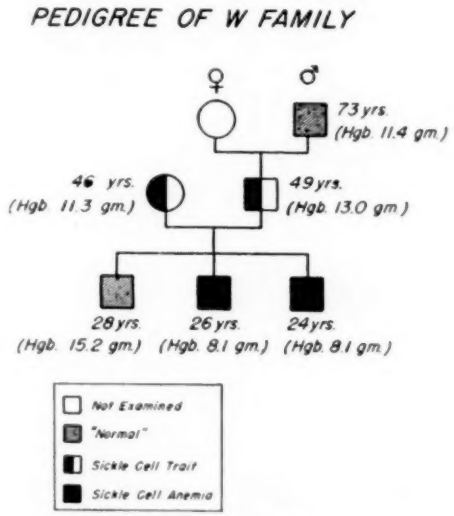

Fig. 2.—Age, hemoglobin value, and sickling status of members of W family.

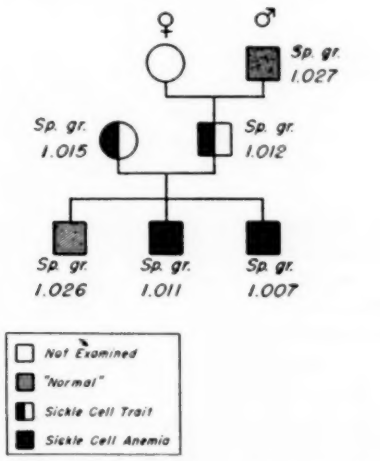

Fig. 3.—Results of 18-hour urine concentration tests in members of W family.

°Kindly performed by Dr. Karl Singer, Chicago, Illinois.

with sickle cell trait but not in those with the thalassemic trait alone.

Discussion. These studies indicate that with few exceptions sicklemic individuals are unable to concentrate urine normally, although clinical tests of renal function yield no other evidence of impaired renal function. Poor concentrating power was present in all 16 patients with sickle cell anemia and in 32 of 36 subjects with sickle cell trait. Parallel findings were obtained in the urine osmotic pressure studies. According to Leaf *et al.*[11] normal subjects can achieve values of 1000 to 1200 mOsm. per liter, or more, under similar test conditions. In this group of sickle cell anemia patients, therefore, the mean osmotic pressure of 421 mOsm. per liter is about half that of normal individuals. The maximum urine osmotic pressure in 32 of the sickle cell trait individuals ranged from 413 to 746 mOsm. per liter. The remaining 4 patients with sickle cell trait reached maximum osmotic urine pressures ranging from 909 to 980 mOsm. per liter. The mean maximum urine osmotic pressure for the entire group of sickle cell trait subjects was only 604 mOsm. per liter, however. Attempts to increase the urine specific gravity and the urine osmotic pressure by the intramuscular injection of pitressin were unsuccessful.

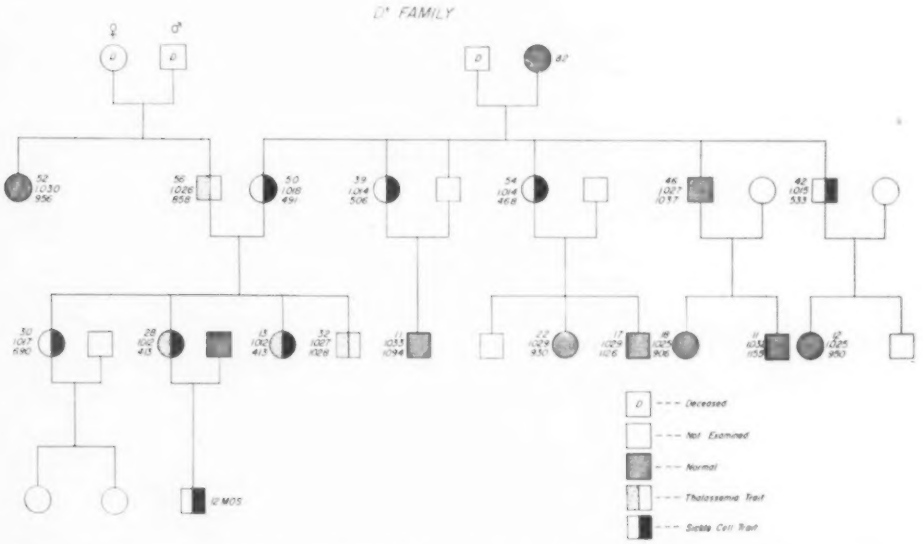

Fig. 4.—Age, specific gravity and osmolarity of urine after fluid deprivation for 18 hours in members of D' family. Note low specific gravity and osmolarity is present only in those individuals who have sickle cell hemoglobin.

The Hickey-Hare tests which were performed in 9 of these subjects clearly indicated that the pituitary-osmoreceptor response was normal. Failure of these patients to concentrate urine normally, therefore, is attributed to dysfunction of the renal tubules.

The role of low hemoglobin values was considered in connection with this phenomenon, but could not be implicated as the cause of poor urine concentration since it was observed in at least 7 trait individuals who had hemo-

globin values ranging from 13 to 15.5 gm. Conversely, the highest urine specific gravity of 1.029 with an osmotic pressure of 909 mOsm. per liter was obtained in a subject with 9.5 gm. of hemoglobin. Furthermore, patients with thalassemia minor and other equivalent long-standing anemias of nonsickle origin fail to show a comparable defect in the urine concentration function.

In some respects, persistence of fetal type kidney function (McCance[13]) is suggested by this observation. The findings differ from the fetal kidney, however, in that sickle cell individuals are able to excrete very dilute urine following hydration (Fig. 1). Thus, the specific gravity is not fixed as was formerly believed (Henderson[5]).

Sicklemic patients may, of course, have various forms of renal disease superimposed on this apparent hyposthenuric defect. In this connection, it may be noted that we have been able to find only one instance of renal calculus in a sickle cell patient and that was associated with pyelonephritis. It may be, therefore, that the presence of a poor concentration function offers some degree of protection against the formation of renal calculi in sickle cell patients. In this connection it may be pointed out that a lower incidence of renal calculi has been observed in Negroes than in the white race (Lattimer[10]).

The syndrome of primary aldosteronism, recently described by Conn[2], also is characterized by limited urine concentration function. The associated serum electrolyte disturbances of aldosteronism were not present, however, in these sickle cell subjects.

It is of interest that hyposthenuria may be related to the pathogenesis of crisis in sickle cell anemia. Sharpsteen[14] has presented evidence that *in vivo* sickling is influenced by differences in the protein osmotic pressures between erythrocytes and plasma. Since diminished capacity to concentrate urine predisposes to dehydration and relative hemoconcentration, the renal defect detected in these patients may contribute to the development of increased plasma osmotic pressure. According to Sharpsteen's theory, factors tending to increase osmotic pressure enhance sickling and possibly precipitate the syndrome of sickle cell crisis.

Thus, of 52 individuals studied, whether sickle cell trait or sickle cell anemia, 48 have exhibited a defect in urine concentration function. That this phenomenon may have a genetic basis is suggested by its uniformity of occurrence and may be supported by the findings in 3 generations of the W family (Figs. 2 and 3) and also in 3 generations of the D' family (Fig. 4). There were, however, 4 sickle cell trait individuals who were able to reach maximum urine osmotic pressures in excess of 900 mOsm. per liter. From a genetic standpoint, these exceptions could be explained on the basis of diminished gene penetrance, or possibly through crossing over of the affected gene. Recent studies by Keitel and Thompson[8] have confirmed our finding of poor renal concentration function in sickle cell trait as well as sickle cell anemia. These workers found, however, that the renal concentration disability could be modified by multiple transfusions with prolonged maintenance of the hematocrit at 40% or better. Not all subjects so transfused experienced improvement in the renal concentrating power, however. Thus, the defect which is exhibited by sicklemic individuals is probably physiologic or metabolic in nature, rather than anatomic. Its presence does not depend on the simultaneous occurrence of anemia, but it is associated with the presence of sickle cell hemoglobin. It appears, therefore, to be inherited as part

of the over-all picture of the sicklemic state.

Whatever ultimately proves to be the basis for this finding, however, it seems strange that such a simply detected defect remained undiscovered for so long. Possibly, the lack of evidence for impairment of other renal functions was an important deterrent in this connection. For example, determinations of glomerular filtration rate, effective renal plasma flow, effective renal blood flow, and tubular excretory capacity for para-aminohippurate were made by Brandt[1] in 9 cases of sickle cell anemia, and by Etteldorf *et al.* in 8 children[3] and 10 adults[4] with sickle cell anemia. Supranormal values were obtained with these more precise tests for renal hemodynamics. Unfortunately, specific gravity and osmolarity tests were not included in their studies. Attention should be called to the fact that Kunz and his colleagues[9] did independently note the impairment of urinary concentration in sickle cell anemia and attributed this phenomenon to a renal defect. Their observations, however, were not extended to sickle cell trait individuals.

Summary. 1. Renal function studies were performed in 16 patients with sickle cell anemia, 33 with sickle cell trait, 2 with mixed sickle cell trait-thalassemia trait, and 1 with mixed sickle cell and hemoglobin C traits.

2. Mean values for the clinical tests of renal function were well within limits of normal for all groups.

3. Limited ability to excrete a concentrated urine after fluid deprivation for 18 hours was the most striking finding.

4. This defect was more pronounced in sickle cell anemia than in sickle cell trait subjects: the mean maximum urine osmotic pressure was 421 mOsm. per liter in the former, and 604 mOsm. per liter in the latter.

5. Reasons for considering the lesion to be renal, of physiologic or metabolic nature, and inheritable as part of the sicklemic state are presented.

ACKNOWLEDGMENTS. Grateful appreciation is expressed to Mrs. Sarah K. Cary, Mrs. Marjorie I. Robbins, Miss Virginia F. Colville, Miss Roberta Stauffenberg, and Miss Ruth Reuter for technical assistance provided during the course of this study.

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(Interlingua on page 104)

ELECTROPHORETIC STUDIES IN DISSEMINATED AND FIXED LUPUS ERYTHEMATOSUS*

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The plasma protein fractions oscillate within certain limits which are considered as normal in healthy individuals. Under pathological conditions, however, these oscillations may become more or less enhanced. In order to investigate such variations, we have been co-ordinating clinical and electrophoretic studies in several diseases[3,12] in which changes of protein concentrations have been disclosed by chemical determinations.

In the present paper we describe the electrophoretic patterns of the blood in 6 cases of disseminated and 12 of the fixed type of lupus erythematosus, with complete clinical observations, laboratory examination findings and courses of treatment. We have endeavored, in particular, to co-ordinate the electrophoretic patterns with the clinical and laboratory findings which permit the interpretation of the results according to the degree of evolution of the disease.

Material and Methods. The patients came from the ward of Professor Aguiar Pupo in the Hospital das Clinicas, of the Faculty of Medicine of the University of São Paulo. Blood was obtained by venipuncture and collected in oxalate, separating the plasma by centrifugation. Laboratory and clinical examinations were performed by the customary methods. The electrophoretic analyses were performed in a Tiselius apparatus according to the method described by two of us[13].

Case Reports. CASE 1. September 12, 1951. The patient was a 32-year-old Japanese woman who had her first lesions 3 years ago. There were erythematous infiltrated lesions on the hands, purpuric petechial lesions on digital pulps, and ungual dystrophies. She complained of loss of weight, general depression, articular pains, insomnia and fever. Physical examination revealed limitation of articular movements, hyperemia and hypertrophy of tonsils and the lymphoid follicles at the base of the tongue, congestion of the vocal cords, and nonspecific vaginitis and radiological evidence of interlobar pleuritis on the right side. Follow-up examinations from September 15, 1951, to May 5, 1952, revealed that the cutaneous lesions and general symptoms disappeared after 3 months. Treatment consisted of 0.2 gm. BCG weekly from September 14, 1951, to December 17, 1951, totaling 2.6 gm. Laboratory examinations showed the following: Mantoux test + at 10^6 on October 30, 1951, ++ at 10^2 on May 5, 1952. Hemograms showed leukocytosis, lymphocytosis and deviation to the left. Tests for LE cells were negative on October 5, 1951, and on May 8, 1952. Serum protein A/G ratios ranged from 1.5 to 1.9 (see Table 1). Liver function tests showed the

*This paper was read at the June, 1952, meeting of the São Paulo Medical Association.

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flocculation tests positive; the Weltmann test was normal. Streptococcic sensitivity was not tested. The urine showed 6 to 8 degenerate leukocytes per field.

CASE 2. August 21, 1951. The patient was a 36-year-old Brazilian woman. Her first lesions appeared 14 months ago. The lesions were infiltrated and hyperpigmented with adherent scaly crusts, follicular lesions with horny spicules, and swelling and ulceration of the lips. She complained of asthenia, anorexia, loss of weight, articular pains, insomnia, fever, night sweats, precordial oppression, 1952, totaling 9.8 gm. The Mantoux test was + at 10^7 on October 31, 1951, and ++ at 10^5 on August 26, 1952. The blood showed lymphocytosis, with deviation to the left, neutrophils with toxic granulations and leukopenia. Serum protein A/G ratios were 0.5 and 0.8 (see Table 1). LE cells were positive up to June 27, 1952; negative on August 7, 1952. Liver function flocculation tests were positive; the Weltmann test reacted up to the 10th tube. Streptococcic sensitivity was negative. Albumin was present in the urine.

CASE	DISSEM. TYPE	ALBUMIN	GLOBULIN					TOTAL PROTEIN
			ALPHA$_1$	ALPHA$_2$	BETA	FIBR.	GAMMA	
nº 1. 6-9-51		4,86	0,34	0,64	0,71	0,55	0,72	7,82
19-9-51		4,94	0,34	0,64	0,78	0,56	0,88	8,14
5-5-52		5,22	0,34	0,68	0,83	0,57	1,02	8,66
nº 2. 22-8-51		3,48	0,38	0,77	0,73	0,96	3,08	9,50
12-9-51		3,45	0,38	0,73	0,67	0,95	2,96	9,14
nº 3. 5-12-51		4,06	0,32	0,74	0,74	0,70	1,42	7,98
nº 4. 5-1-52		3,79	0,30	0,67	0,57	0,53	1,14	7,00
nº 5. 29-12-51		4,32	0,39	0,76	0,74	0,66	1,31	8,18
nº 6. 5-12-51		2,14	0,37	0,93	0,82	0,69	1,14	6,09
NORMAL		4,70	0,30	0,55	0,90	0,40	0,90	7,75

Table 1.—Electrophoretic studies in disseminated lupus erythematosus.

and dyspnea after exertion. Physical examination revealed palpebral edema, masculine distribution of hair, polyadenomegaly, blood pressure 140/90, nodosities in axillary and humeral arteries, enlarged hilus with small nodular calcifications, slight velamen of right apex, and radiological evidence of the bone alterations of rheumatoid arthritis. Follow-up examinations from June 6, 1951, to September 9, 1952, showed disappearance of cutaneous lesions and general symptoms, and a 9-kg. gain in weight after 7 months. Treatment was given with oral BCG 0.2 gm. weekly from September 6, 1951, to September 16,

CASE 3. November 29, 1951. The patient was a 34-year-old Brazilian woman. Erythematous infiltrated lesions in butterfly form and follicular horny spicules occurred 2 years ago. She complained of general depression, articular pains, palpebral edema, and stinging pain in left hemithorax. Physical examination revealed polyadenomegaly, diminished respiratory expansion of left hemithorax, palpebral edema, swelling, heat and redness of articulations, opacity of external half of upper lobe of right hemithorax, discrete epiphyseal osteoporosis. Follow-up examinations from December 4, 1951, to August 29, 1952,

revealed nearly complete disappearance of cutaneous lesions and improvement of her general state after 9 months. Treatment with oral BCG 0.2 gm. weekly from December 4, 1951, to July 21, 1952, was without result, and 200 mg. cortisone daily was given from July 9, 1952, to October 11, 1952. Mantoux test was negative. Hemograms showed deviation to the left and toxic granulations in the neutrophils. LE cells were positive up to May 21, 1952, and negative on July 23, 1952, after transfusion. Serum protein A/G ratios were 1.1 and 2.0 (see Table 1). Liver function flocculation tests were positive. The Weltmann test was normal. Streptococcic sensitivity was negative. Albuminuria with 2 to 4 leukocytes and 2 to 3 erythrocytes per field was present.

CASE 4. December 27, 1951. The patient, a 16-year-old Brazilian woman, had her first lesion 4 months ago. The lesions were erythematous and infiltrated with protruding edges on face and skull, ulcerations with punctiform hemorrhage on lips and gums and hemorrhagic periungual ulcerations. She complained of general depression, articular pains and swelling, pectoralgia, and pains in left hypochondrium. Physical examination revealed polyadenomegaly, swollen, painful and reddish joints, pronounced jaundice, hepatomegaly, splenomegaly, infiltration of right base, velamen of right diaphragmatic sinus, and systemic osteoporosis. From December 27, 1951, to June 4, 1952, there was great improvement of the cutaneous lesions but persistence of the general state of ill health after 6 months. She was treated with oral BCG 0.2 gm. weekly from January 22, 1952, to June 4, 1952, a total of 3.8 gm. The Mantoux test was + at 10^6 on December 28, 1951, and + at 10^3 on March 21, 1952. Examination of the blood revealed an eosinophilia, hypochromia and neutrophils with toxic granulations. LE cells were present. Serum protein A/G ratios were 1.1 and 1.7 (see Table 1). Liver function flocculation tests were positive. The Weltmann test was normal. Streptococcic sensitivity was positive on January 17, 1952, and negative on March 21, 1952. Albuminuria with an abundance of leukocytes and erythrocytes was present.

CASE 5. December 17, 1951. The patient, a 60-year-old Italian man, had his first lesions 2 years ago. There were erythematous infiltrations with scales on the face, neck, mediastinal region, back and forearms, and residual xanthomatous lesions on the extremities. He complained of articular pains, fever, asthenia, pruritic lesions, and attacks of giddiness. Physical examination revealed a precarious general state, a blood pressure of 180/100 with splitting of the first sound at the mitral area, and cochlear degeneration. Follow-up examinations from December 17, 1951, to September 27, 1952, showed involution of cutaneous lesions with slight relapse and disappearance of the general symptoms. He was treated with 0.2 gm. of BCG by mouth weekly from December 17, 1951, to September 23, 1952, a total of 7.0 gm. The Mantoux test was + at 10^7 on November 19, 1951, and + at 10^5 on August 5, 1952. The blood showed a leukopenia, deviation to the left and eosinophilia in the beginning, turning to aneosinophilia, toxic granulations and thrombocytopenia on July 1, 1952. On December 14, 1951, LE cells were negative, becoming positive on February 14, 1952, and remained so until July 8, 1952. Serum protein A/G ratios were 1.1 and 1.3 (see Table 1). Liver function flocculation tests were slightly positive. The Weltmann test was normal. Streptococcic sensitivity was negative. Albuminuria was present but disappeared after January 10, 1952.

CASE 6. July 24, 1951. The patient, a 23-year-old Brazilian woman, had no cutaneous lesions. She complained of fever, stinging pains in the left hemithorax, buzzing in the ears, anorexia and dyspnea after exertion. Examination revealed palpebral edema, adenomegaly, increase of fremitus, and a massive left base, myocardial involvement (electrocardiograph) and pleural effusion at the left base. From July 24, 1951, to January 1, 1952, there was accentuation of palpebral edema, dyspnea and hypertension. She was treated with cortisone, vitamin E, antihistaminics and streptomycin. The Mantoux test was + at 10^7 (August 31, 1951). The blood showed leukopenia, deviation to left, neutrophils with toxic granulations, eosinophilia and hypochromia. Test for LE cells was positive. Serum protein A/G ratios were 0.8 and 1.2 (see Table 1). Liver function flocculation tests were positive. The Weltmann test was slightly shortened. Streptococcic sensitivity was not tested. There was albuminuria with some degenerated leukocytes and a few erythrocytes per field.

CASE 7. July 19, 1951. The patient, a 37-year-old Brazilian woman, had her first lesions 5 years ago. There were erythematous scaly lesions on the face, ears, sternal region, side of neck and occipital region and pigmentary lesions with atrophy on the forearms. She complained of itching lesions. Clinical examination disclosed nothing noteworthy. Follow-up examinations from August 29, 1951, to November 25, 1952, showed atten-

uation of lesions, disappearance of scales and reduction of infiltrations. Treatment consisted of oral BCG 0.2 gm. weekly from August 29, 1951, to October 17, 1952, (a total of 8.2 gm.) with several interruptions due to gastric intolerance. The Mantoux test was +++ at 10^2 on August 2, 1951, and ++++ at 10^3 on August 11, 1952. The blood showed leukopenia,, deviation to the left, and eosinophilia. No test for LE cells was made. Serum protein A/G ratios were 1.7 and 1.9. (See Table 2). Liver function late, bismuth, gold salts and oral BCG 0.2 gm. weekly from August 20, 1951, to July 3, 1952 (a total of 6.2 gm.), quinacrine from December 6, 1952, to February 27, 1953. The Mantoux test was ++ at 10^3 on August 21, 1951, and +++ at 10^3 on November 20, 1952. The blood showed lymphocytosis and neutrophils with toxic granulations. LE cells were negative. Serum protein A/G ratios ranged from 1.5 to 1.8 (see Table 2). Liver function flocculation tests were essentially normal. Streptococcic sensitivity showed 10-

CASE	FIXED TYPE	ALBUMIN	GLOBULIN					TOTAL PROTEIN
			ALPHA,	ALPHA,	BETA	FIBR.	GAMMA	
nº 7 22-8-51		4,25	0,33	0,56	0,82	0,68	0,89	7,53
4-10-51		5,01	0,33	0,75	0,84	—	0,96	7,89
nº 8 22-8-51		5,28	0,30	0,58	0,82	0,63	1,30	8,91
4-10-51		5,09	0,31	0,56	0,81	—	1,20	7,97
11-2-52		5,10	0,28	0,50	0,55	0,90	1,17	8,50
nº 9 22-8-51		4,84	0,32	0,77	1,18	0,61	1,06	8,78
nº 10 27-10-51		4,48	0,28	0,67	0,58	0,38	0,71	7,10
nº 11 24-8-51		5,15	0,37	0,74	0,99	0,59	0,99	8,83
nº 12 4-10-51		4,95	0,34	0,66	0,78	—	0,79	7,52
nº 13 25-10-51		4,54	0,35	0,78	0,78	0,72	0,90	8,07
13-3-52		5,00	0,29	0,67	0,78	0,75	1,21	8,70

Table 2.—Electrophoretic studies in fixed lupus erythematosus.

flocculation tests were slightly positive. The Weltman test was shortened. There was streptococcic sensitivity: 10-minute reading negative, 24-hour reading positive (+). The urine was normal.

CASE 8. December 7, 1950. The patient, a 22-year-old Brazilian woman, had her first lesions 5 years ago. There were erythematous scaly lesions on nose and sternal region. She had no complaints. Physical examination revealed nothing of significance. Follow-up study from August 20, 1951, to July 3, 1952, showed no alteration of the lesions. She was treated with sodium salicy-

minute reading negative, 24-hour reading positive (++). The urine was normal.

CASE 9. June 12, 1951. The patient, a 52-year-old Brazilian woman, first had lesions 2 years ago. There were patches with infiltrated edges and atrophic centers on the nose and malar regions. She complained of a burning sensation at the cutaneous lesions. Examination revealed a normal blood pressure (155/95), an accentuated second aortic sound, Duplay's disease (subacromial or subdeltoid bursitis) and articular pains. Follow-up study from June 12, 1951, to March 1, 1953, showed complete disappearance of the

cutaneous lesions. She was treated with oral BCG 0.2 gm. weekly from July 2, 1951, to October 1, 1952, a total of 13.6 gm. The Mantoux test was ++ at 10^3 on June 12, 1951, and March 4, 1952. The blood showed eosinophilia, deviation to the left, and lymphocytosis. Serum protein A/G ratio was 2.0 (see Table 2). No test for LE cells was made. Liver flocculation tests were negative. The Weltmann coagulation band extended to the 5th tube. Streptococcic sensitivity was not tested. The urine was normal.

CASE 10. May 30, 1951. The patient, a 30-year-old Brazilian man, first had lesions 6 months ago. The lesions were erythematous and swollen in butterfly form and there were papulous lesions on the sides of the neck. He complained of frequent headaches, periodic diarrhea, and itching lesions. Physical examination revealed nothing worth noting. Follow-up study from September 12, 1951, to February 23, 1953, showed the lesions no longer infiltrated but still erythematous. He was treated with oral BCG 0.2 gm. weekly from September 14, 1951, to December 6, 1951. Treatment with BCG was then abandoned. On January 21, 1953, treatment was started with metoquina (an antimalarial drug), 3 tablets daily, and tocopherol 200 mg. daily. The Mantoux test was + at 10^3 on August 29, 1951. The blood showed neutrophils with toxic granulations, deviation to the left, eosinophilia and thrombocytopenia. No test for LE cells was made. Serum protein A/G ratios were 2.2 and 2.8 (see Table 2). Flocculation tests for liver function were slightly positive; the Weltmann test reacted to the 4th tube. Streptococcic sensitivity was not tested. The urine was normal.

CASE 11. August 22, 1951. The patient, a 44-year-old Brazilian man, had his first lesions 7 years ago. There were erythematous scaly and infiltrated patches in the malar region. He complained of itching and burning lesions. Physical examination revealed an acute catarrhal conjunctivitis. Follow-up study from August 27, 1951, to February 11, 1953, showed attenuated but persistent lesions. He was treated with oral BCG 0.2 gm. weekly from August 27, 1951, to February 11, 1953, a total of 12.4 gm. The Mantoux test was + at 10^3 on August 24, 1951, and October 15, 1952. The blood showed neutrophils with toxic granulations, and deviation to the left. No test for LE cells was made. Serum protein A/G ratios were 1.9 and 2.2. Liver function flocculation tests were slightly positive; the Weltmann coagulation band extended to the 3rd tube. Streptococcic sensitivity was positive (+) at 24-hour reading. The urine was normal.

CASE 12. December 18, 1950. The patient, a 56-year-old Brazilian man, had his first lesions 2 years ago. There were numerous erythematous lesions, infiltrated and with adherent scales in the center. He complained of general weakness and loss of weight. Physical examination revealed congestion of pharyngeal-laryngeal mucous membranes, hypertrophy of lymphoid follicles at the base of the tongue, altered pigmentation of the retina with narrowed vessels. Follow-up study from December 18, 1950, to March 5, 1953, showed reactivation of lesions up to October 17, 1951, thereafter, a diminished infiltration. He was treated with vitamin B_1 for one month, vitamin E, and sodium salicylate. Oral BCG 0.2 gm. weekly was given from October 17, 1951, to August 11, 1952, a total of 9.0 gm. The Mantoux test was + at 10^4 on December 19, 1951, and ++ at 10^3 on September 4, 1952. The blood showed lymphocytosis, neutrophils with toxic granulations, deviation to the left and eosinophilia. No test for LE cells was made. Serum protein A/G ratios were 1.8 and 2.3 (see Table 2). Liver function flocculation tests were negative. The Weltmann coagulation band extended to the 3rd tube. Streptococcic sensitivity was negative. The urine was normal.

CASE 13. May 30, 1951. The patient, a 58-year-old Brazilian woman, had her first lesions 2 years ago. She complained of weakness and loss of weight. Physical examination revealed hypertension (200/100), accentuated second sound at the base, bubbling rales in the interscapular-vertebral region. Follow-up study from May 30, 1951, to March 5, 1953, showed disappearance of the cutaneous lesions. She was treated with BCG 0.2 gm. weekly from October 20, 1951, to January 7, 1952, a total of 2.0 gm., and with vitamin E and quinacrine. The Mantoux test was ++ at 10^3 on October 12, 1951, and + at 10^4 on October 2, 1952. The blood showed neutrophils with toxic granulations and eosinophilia. No test for LE cells was made. Serum protein A/G ratio was 2.5 (see Table 2). Liver function flocculation tests were negative. The Weltmann test reacted to the 4th tube. Streptococcic sensitivity was positive (++) on 24-hour reading. There was albuminuria with a few isolated or grouped degenerated leukocytes and erythrocytes.

CASE 14. October 9, 1951. The patient, a 40-year-old Brazilian woman, had her first lesions 4 years ago. The lesions were erythematous, scaly and infiltrated on the face, scalp and anterior and posterior regions of the

trunk. She complained of itching and burning lesions. Physical examination revealed nothing worth noting. Follow-up study from October 19, 1951, to February 5, 1953, showed progressive improvement after BCG. She was treated with sodium salicylate and vitamin E. Oral BCG 0.2 gm. was given weekly from October 30, 1951, to August 26, 1952, a total of 8.0 gm. Cortisone was also administered. The Mantoux test was + at 10^4 on October 10, 1951, and on June 2, 1952. The blood showed neutrophils with toxic granulations, deviation to the left, eosinophilia and leukopenia. LE cells were not present. Serum protein A/G ratios were 1.5 and 1.8 (see Table 3). Liver function flocculation tests were negative. The Weltmann coagulation band extended to the 5th tube. Streptococcic sensitivity was strongly positive (+++) at 48-hour reading. The urine showed a few degenerated leukocytes.

CASE 15. October 25, 1951. The patient, a 47-year-old Lithuanian woman, had her first lesions 4 years ago. There were spreading and erythematous infiltrated lesions on the face. She complained of itching cutaneous lesions. Physical examination revealed increase of cardiac area at the expense of the right atrium. Follow-up study from October 29, 1951, to March 10, 1953, showed improvement and reduction of infiltration. Treatment with sodium salicylate, vitamin E, chrysalbine (a gold preparation), and oral BCG 0.2 gm. weekly from November 20, 1951, to June 10, 1952, a total of 6.0 gm. The Mantoux test was +++ at 10^2 on November 19, 1951, and + at 10^3 on December 16, 1952. The blood showed leukopenia, eosinophilia and deviation to the left. There were no LE cells. Serum protein A/G ratios were 1.5 and 1.7 (see Table 3). Liver function tests were normal. Streptococcic sensitivity was negative. The urine was normal.

CASE	FIXED TYPE	ALBUMIN	GLOBULIN					TOTAL PROTEIN
			ALPHA,	ALPHA,	BETA	FIBR.	GAMMA	
nº 14 5-10-51		4,19	0,33	0,81	0,97	0,72	0,86	7,88
29-3-52		4,47	0,36	0,71	0,88	0,44	0,91	7,77
nº 15 25-10-51		5,02	0,36	0,76	0,90	0,69	1,08	8,81
27-3-52		4,88	0,31	0,67	0,95	0,83	1,15	8,79
nº 16 1-12-51		4,62	0,25	0,85	0,85	0,75	1,04	8,36
nº 17 31-1-52		4,89	0,33	0,61	0,76	0,70	1,01	8,30
nº 18 1-2-52		4,94	0,30	0,53	0,67	0,53	0,78	7,75
13-3-52		4,64	0,26	0,55	0,65	0,58	0,76	7,44
31-3-52		4,64	0,26	0,51	0,60	0,54	0,77	7,32

Table 3.—Electrophoretic studies in fixed lupus erythematosus.

CASE 16. November 22, 1951. The patient, a 30-year-old Brazilian woman, had her first lesions 9 months ago. There were numerous erythematous scaly lesions on the face, nodular fistulated lesions on submaxillary region (scrofuloderm). She complained of itching and burning lesions, general weakness, cough, expectoration and a recent attack of serofibrinous pleurisy. Physical examination revealed larger expansion of right hemithorax, thoracic vocal fremitus increased on left base, diminution of sound and few crepitant rales in the left hemithorax, reinforced vasobronchial texture, and thickened pleura. Follow-up study from November 22, 1951, to March

12, 1953, showed improvement of general state, increase in weight and scarring of fistular lesions but no alteration of facial cutaneous lesions. She was treated with oral BCG 0.2 gm. weekly from November 25, 1951, to December 16, 1952, a total of 6.4 gm. The Mantoux test was ++ at 10^6 on November 23, 1951, and ++ at 10^5 on January 9, 1953. The blood showed neutrophils with toxic granulations and eosinophilia. LE cells were negative. Serum protein A/G ratios were 1.3 and 2.4 (see Table 3). Liver function tests were negative. Streptococcic sensitivity was positive (+) on 48-hour reading. The urine was normal.

CASE 17. January 16, 1952. The patient, a 21-year-old Brazilian man, had his first lesions 2 years ago. There were erythematous scaly infiltrated patches with central atrophy and peripheral pigmentation in malar regions. He complained of a burning sensation in the lesions on exposure to sunlight. Physical examination disclosed nothing noteworthy. Follow-up study from November 26, 1951, to June 19, 1952, showed atrophic scars surrounded by circinate pigment bands. He was treated with oral BCG 0.2 gm. weekly from January 29, 1952, to October 16, 1952. The blood showed neutrophils with toxic granulations and deviation to the left. No test

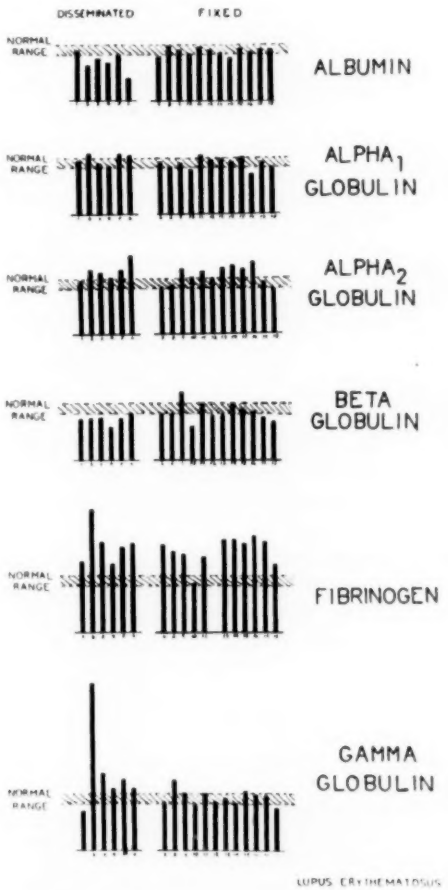

Table 4.—Plasma proteins before treatment.

was made for LE cells. Serum protein A/G ratios were 1.9 and 2.1 (see Table 3). Liver function tests were negative. The Weltmann test was normal. No test for streptococcic sensitivity was made. The urine was normal.

CASE 18. January 24, 1951. The patient, a 38-year-old Brazilian woman, had her first lesions 4 years ago. There were erythematous infiltrated lesions on face, occipital region, body and neck. She had no complaints. Physical examination revealed evidence of interlobar pleuritis on the right side and a thickened right hilus. Follow-up study from January 24, 1952, to March 13, 1953, showed complete disappearance of the cutaneous lesions. Treatment was given with oral BCG 0.2 gm. weekly from March 3, 1952, to July 13, 1952, a total of 3.8 gm. The Mantoux test was negative at 10^3 on January 25, 1952, +++ at 10^3 on September 2, 1952. The blood showed lymphocytosis, deviation to the left, and neutrophils with toxic granulations. LE cells were negative. Serum protein A/G ratios ranged from 1.3 to 2.4 (see Table 3). Liver function tests were negative. The Weltmann test was not done. Streptococcic sensitivity was not tested. The urine was normal.

Results. Tables 1, 2, 3, and 4, show the results of the electrophoretic analyses of our cases, the first 6 being of the disseminated and the other 12 of the fixed type of lupus erythematosus.

Discussion. It may be stated that very little had been written about plasma proteins in acute disseminated lupus erythematosus before 1942[5].

In 1932, Reifenstein *et al.*[15] mentioned, for the first time, hyperglobulinemia and hyperproteinemia in this disease, and in 1935, Baehr *et al.*[2] reported 2 cases of hypoproteinemic edema.

However, it was in 1942 that Taussig[17] first measured protein concentration, finding increases in 8 of 9 patients.

Coburn and Moore[5], in 1942, studied the plasma proteins in 15 patients, with normal proteinemia and inversion of the A/G ratio in most cases. All showed a fall of albumin and hyperglobulinemia. In 2 cases which were submitted to electrophoresis, the hyperglobulinemia could be traced to the gamma globulin. They tried to interpret the hypergammaglobulinemia as a cause of the disease. The same authors observed furthermore that the gamma globulin from cases of lupus erythematosus reacts *in vitro* with the phospholipids of Wassermann and Kline antigens, which could explain the oscillations of serologic tests in certain cases of this disease. Many later publications[1,4,6,7,8,10,14,16] confirmed the hypergammaglobulinemia.

Haserick and Borst[11] described an increased alpha$_2$ globulin fraction in addition to hypergammaglobulinemia.

Walker and Benditt[19] also found an inversion of the A/G ratio and a fall in beta globulin in fixed lupus erythematosus.

Sampaio[18] observed 4 cases with hyperglobulinemia, only two of which had an increased protein concentration.

Gomes[9], in a review of the literature, found 77% of hyperglobulinemia in 44 cases, with normal protein values in 48%.

According to the literature, all cases of lupus erythematosus are accompanied by hypergammaglobulinemia.

In the present study of 18 cases of lupus erythematosus, 6 of which belonged to the disseminated and 12 to the fixed type, we observed as a common trait a decline of albumin and of beta globulin, with increases in alpha$_2$ globulin and fibrinogen. The decrease of albumin and of beta globulin was more pronounced in the disseminated cases, whereas the increase of alpha$_2$ globulin and of fibrinogen was equivalent in both forms. An increase of gamma globulins which had been described by other authors was observed only discretely in 5 of the 6 disseminated and 1 of the 12 fixed cases. The single disseminated case with an exceptional hypergammaglobulinemia was

that of a patient with a lymph-glandular tuberculosis with positive guinea-pig inoculation, exhibiting a pronounced plasmocytosis (10% plasmocytes), besides an increase in fibrinogen. Hyperproteinemia was observed in one of the disseminated and in 4 of the fixed cases. No correlation could be established between the severity of the disease and the gamma globulin levels. Alpha$_2$ globulin was found increased in 4 of the disseminated and 6 of the fixed cases. These findings are in agreement with the data of Haserick and Borst[11].

Special attention should be given to the fact that an increase of alpha$_2$ globulin is far more frequent than a rise in the gamma globulin fraction. It should further be stressed that fibrinogen was found to be increased in all the disseminated and 11 of the 12 fixed cases. This simultaneous increase of alpha$_2$ globulin and fibrinogen is usually found in mesenchymopathies, and constitutes, in our view, a point which ought to be considered of greater significance than the hypergammaglobulinemia. Another factor which should not be overlooked is the constant decrease of beta globulin in all the disseminated and the greater part of the fixed cases; this decrease of beta globulin has also been observed by the authors in the Nicolas-Favre disease[3] and in leprosy[12].

Summary. The authors present the electrophoretic results of 18 cases of lupus erythematosus, 6 of which were of the disseminated and 12 of the fixed type. They observe a general decrease of albumin and of beta globulin, which was more pronounced in the disseminated cases, and an increase of alpha$_2$ globulin and of fibrinogen in both forms. They present the clinical observations and laboratory data of their patients and show the clinical evolution of the cases, with critical considerations on the interpretation of the electrophoretic pattern in each case, some of which indicated a tendency towards normalization of the proteinemia with the improvement of the patients. They find a hypergammaglobulinemia in 5 of the 6 disseminated and one of the 12 fixed cases, with hyperproteinemia in one of the disseminated and in 4 of the fixed cases.

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SUMMARIO IN INTERLINGUA

Studios Electrophoretic in Disseminate e Fixe Lupus Erythematose

Le autores presenta le resultatos electrophoretic obtenite in 18 casos de lupus erythematose. Sex del casos representava le typo disseminate, 12 esseva del typo fixe. Esseva observate un reduction general de albumina e globulina beta, plus pronunciate in le casos disseminate, e un augmento de globulina alpha$_2$ e fibrinogeno, equalmente pronunciate in ambe typos de casos. Le autores presenta le observationes clinic e le datos laboratorial que characterisava le morbo de lor patientes e monstra le evolution clinic del casos individual. Illes presenta considerationes critic relative al interpretation del configurationes electrophoretic obtenite pro le varie patientes. Esseva notate in certe casos un tendentia verso le normalisation del proteinemia, progredente in le curso del melioration del stato del patiente. Le autores constatava hypergammaglobulinemia in 5 del 6 casos disseminate e in un del 12 casos fixe. Hyperproteinemia esseva trovate in un del casos disseminate e in 4 del casos fixe.

SUMMARIO IN INTERLINGUA

(See page 38 for original article)

Le Nivello del Aldolase Seral in Acute Infarcimento Myocardial

1. Trenta-duo canes bastarde esseva subjicite a pericardiotomia. Le branca descendente del sinistre arteria coronari esseva ligate in 12 del animales justo infra le bifurcation. In contrasto con le alte ligation assi producite in le prime 12 animales, un basse ligation esseva executate in un secunde gruppo consistente de 10 animales. Le remanente tertie gruppo de 10 animales serviva como controlo.

2. Le nivellos del aldolase seral esseva studiate quotidiannmente in omne le animales; in duo animales con alte ligation a intervallos de un hora durante 7 e 8 horas respectivemente.

3. Esseva constatate un considerabile e rapide augmento post-operative del aldolase seral in omne canes con ligation coronari. Il esseva possibile establir un relation semiquantitative inter le area del necrose myocardial e le aldolase seral.

4. In un studio clinic preliminari il esseva trovate que 8 patientes con acute infarcimento myocardial habeva un considerabile augmento del aldolase seral, de accordo con le severitate approximative del curso clinic. In 5 patientes con insufficientia coronari le aldolase seral remaneva normal.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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THE PROBLEM OF THE VOLUME COMPONENT OF BODY FLUID HOMEOSTASIS

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CLAUDE BERNARD'S introduction of the principle of the stability of the "milieu interieur" provided impetus for investigative effort of considerable importance. This has afforded at least an insight into regulatory processes concerned with preservation of the *molecular* constancy of extracellular fluid (ECF). On the other hand, surprisingly little attention has been directed toward another aspect of stability, volume constancy of ECF, probably because emphasis has been placed on the individual cellular unit. Admittedly, the amount of fluid surrounding it would seem to be a matter of relative indifference, from the cell's viewpoint, so long as its composition were optimal. From the standpoint of the whole organism, and ultimately the cells, however, a regulation of ECF volume is vitally necessary to guide it between the Scylla of dehydration and the Charybdis of anasarca.

In a system such as the body, a steady state could be achieved by regulating either input or output with respect to the other. Whereas the sensations of thirst and hunger do exert a regulating influence over input, two simple observations tend to minimize their importance with respect to volume regulation. First, in the normal individual, purposeful distortion of body volume by over or underalimentation evokes strong corrective renal responses. Second, in conditions of volume distortion, such as generalized edema, there is no apparent aberration of intake but rather a diminution of output. It is for these reasons that, if we would seek the answer to regulation of ECF volume, we must turn to the kidney for the final pathway. Its efficiency in this regard is implicit in the stability of adult body weight, despite the quantitatively indiscriminate nature of intestinal absorption.

The dual nature of renal function was well appreciated by Starling[34], who in 1909 wrote: "In the kidneys we find an organ whose function, broadly speaking, is the regulation of the amount and composition of the total fluid of the body; a regulation which it is able to carry out in consequence of its sensitiveness to minute changes in composition and amount of blood circulating through its vessels."

The importance of approaching the problem of edema from the standpoint of volume regulation was forcefully expressed by McClean[24] in 1925 and, more recently, by Wolf[42] in 1950. Both gave precise formulation to the problem in terms of "volume distorting" and "volume restoring" forces. Obviously, a real solution can be achieved only by defining these forces in terms of known physicochemical or physiologic processes. In spite of a recent revival of interest in the matter of volume regulation, investigative efforts have succeeded only in destroying certain naive notions[1,3,4,8,29]. It would seem that Peters[29], in describing the link between volume regulation and renal function as one of the most elusive and crucial problems of renal physiology, did not overstate the case.

A grasp of the nature of this problem is attained rather simply when we attempt to trace the sequence of events following ingestion of a quantity of water and compare them with those following ingestion of an equal quantity of a fluid closely approximating ECF in composition. In the first instance, the molecular pattern of ECF is distorted; an osmoreceptor is thereby affected, which, by way of reduced output of a hormonal messenger, modifies renal tubular activity, and a brisk diuretic response ensues. Thus, water is excreted, in a sense, as if it were a foreign substance. If, on the other hand, we ingest the same volume of water, having previously added to it a number of solutes so that its composition becomes more or less identical with ECF, we still get a diuretic response, but less intense and more prolonged. Since, here, we have not altered the nature of body fluid, how does the kidney receive the information upon which it bases its appropriate reaction?

A change in volume is a *capacity* change and as such cannot conceivably activate any mechanism enclosed within it unless it is, by circumstance, capable of being converted into an *intensity* change. For example, thermoregulatory devices are not activated by the *amount* of heat surrounding them but rather by the *intensity* of heat as manifested by changes in temperature. Pressure is the intensity factor that is related to volume in the same way that temperature is to heat.

That pressure or the stretching of some volume compartment is in some way involved is suggested by the fact that continuous ingestion of isotonic sodium chloride solution at a rate of 500 ml. per hour will increase urinary output slowly but in asymptomatic fashion until it nearly equals the rate of intake. At this point, a tendency toward a biologic steady state is achieved. The body weight, which has been rising, will now tend to remain constant. The sluggish renal response to small initial changes in volume would appear to be related in some way to the relative "looseness" or "laxness" of body tissue, or some components thereof, which needs to be overcome before a strong diuretic stimulus is evoked. This tendency to yield initially to a distorting force without opposition has been described in inanimate systems, where it has been termed hysteresis.

Attempts to locate "baroreceptor" or "stretch receptor" mechanisms have been numerous[13], and the whole matter

has been ably reviewed by Bull[8], who concludes that none capable of acting as volume regulators has as yet been found. Even if their existence were assumed, the necessity for neural or hormonal-transmitting mechanisms would arise. The possibility of direct neural control is excluded by the fact that transplanted kidneys serve adequately as volume regulators[12,26]. The possibility of hormonal transmitters is suggested by the well-known sodium-retaining properties of certain steroids. However, as pointed out by Borst[4], their effect is accompanied by increased excretion of potassium. This pattern is not seen in the sodium retention associated with either decreased volume or a state of circulatory inadequacy by other cause. Although he believes it unlikely that such hormones control volume regulation, Borst does advance a tentative hypothesis that heretofore undescribed hormone may be elaborated within the kidney itself, controlled in some way by the flow of blood through this organ.

Luetscher and Johnson[22] reported increased urinary output of aldosterone in patients with edema and suggested that the stimulus may be a state of circulatory inadequacy. It would appear more likely that the increased output of this hormone is conditioned by the tendency toward hyponatremia that exists in patients with expanding ECF volumes, since even the normal dietary intake is hypotonic with respect to sodium. This was clearly illustrated when the syndrome of primary aldosteronism due to overproduction of this hormone was shown not to be characterized by edema[10]. If we wish to indulge in the pasttime of inventing hormones, or of ascribing to existing hormones the power to exert regulatory function, we must also bear the responsibility for suggesting receptor mechanisms capable of reacting to appropriate stimuli.

Peters, in 1935[30], suggested that the fullness of the blood stream might provoke the diuretic response on the part of the kidneys. This concept has been amplified by Borst[3,4], who believed that whenever a condition of circulatory inadequacy exists, there is a tendency on the part of the kidney to retain fluid. The increased blood volume consequent to this retention is thought to result in increased cardiac output until circulatory adequacy is restored. During states of circulatory excess, such as might be encountered by infusion of plasma or blood into normal individuals, or occasionally when tachycardia occurs in an otherwise normal heart, a diuretic response has been observed. These observations and others by Borst[3,4], and his penetrating analysis of them, constitute one of the most lucid expositions on the problem of volume regulation. Unfortunately, they do not provide us with details of renal participation in this process.

Decades ago, renal physiologists had a simple, ready explanation for the diuresis produced by administration of isotonic saline[11]: They reasoned that, as a consequence of the dilution of plasma proteins, glomerular filtration would proceed at a more rapid rate, thus yielding enhanced urinary flows. This simple explanation appeared to be reinforced by Knowlton's[19] demonstration that saline diuresis could be inhibited by adding to the infusion oncotically active substances, such as acacia or gelatin.

This view remained essentially unchallenged until 1940, when Eggleton, Pappenheimer, and Winton[14] observed that in the anesthetized dog isotonic saline diuresis was accompanied by little change in glomerular filtration rate. Furthermore, the diuretic response was much greater when effective glomerular filtration pressure was in-

creased by a diminution in oncotic pressure than when a similar change was produced by a rise in arterial pressure. This was true even though a disproportionate elevation of rate of filtration occurred in the latter instance.

Since this time, other evidence has been gathered that suggests that renal response to alterations in volume is mediated largely at a tubular rather than glomerular level. In particular, the experiments of Strauss and associates[35] and Black and co-workers[2] are altogether convincing in this regard. The first group demonstrated that when ECF is expanded with hypotonic solutions, the rate of sodium excretion is *increased*, despite the fact that filtered load of sodium is *decreased*. The second group demonstrated that in salt-depleted individuals the increase of serum sodium to normal or supernormal values, although resulting in high filtered loads of sodium, failed to produce a significant natriuretic response. In addition to highlighting the role of tubular reabsorption as the determinant of the rate of sodium excretion, these experiments were further instructive in that they required the kidney to defend either the volume of ECF or the molecular constancy of this fluid. The response in each case, although probably a compromise, was in favor of volume of ECF, suggesting that separate tubular mechanisms exist for volume and molecular regulation. This problem has been ably discussed by Leaf and Mamby[21]. Depending on circumstances, these may operate in the same or opposing directions, the ultimate urinary composition being a reflection of the contribution of each. Because of the hypotonic nature of even the ordinary diet, congestive heart failure has been suggested to exemplify the two regulatory mechanisms acting in opposition[6].

Much of the conceptual difficulty with regard to the problem of volume regulation arises from the current belief that tubular reabsorption of the bulk of filtered fluid is secondary to active reabsorption of sodium, so that volume regulation must be related to the control of an active transport mechanism deriving its energy from metabolic sources. Since volume changes, in themselves, do not cause alterations of the substrate that might, in turn, directly affect metabolism, the necessity arises for postulating improbable and as yet undemonstrable receptor and transmitter systems, as discussed previously.

This limited concept of the nature of tubular reabsorption has its historical derivation in the theory of urinary secretion advocated by Cushny[11] in his monograph published in 1917. It has taken its current form largely from modifications proposed by Wesson, Anslow and Smith[38,39] whose views have been so influential that they deserve detailed comment. They divide sodium reabsorption into two processes, one occurring in the proximal tubule and another at some distal site. The first accounts for approximately 85% of sodium reabsorption, whereas the remaining 15% is acted upon by the distal mechanism, where finer adjustments, in accord with the needs of the organism, may take place. Proximal reabsorption has been shown to be an essentially isosmotic process[37] and, as such, would be a likely locus for volume regulation which itself is, by definition, an isosmotic process. It is, therefore, their views concerning this particular component of sodium reabsorption that are pertinent to the present discussion. Here they conceive of an active transport mechanism as a sort of intracellular pump for sodium and possibly other ions, water following passively along the resulting concentration gradients,

to effect osmotic equilibration. In effect, this would mean that sodium reabsorption within the proximal tubule is to a large extent *operationally* independent of water reabsorption.

The experimental evidence on which they base their views is derived largely from studies of mannitol-induced diuresis in dogs. Assuming that maximal distal tubular reabsorption would not exceed 15% of the filtered sodium load, they reasoned that if high enough urinary flows could be attained the composition of urine would approach that of the fluid leaving the proximal tubule. They succeeded in inducing rates of urinary flow that constituted as much as 65% of filtered fluid. Analysis of these urines revealed that only 13 to 27% of the filtered sodium was excreted. Since urinary composition was considered a good approximation of the fluid leaving the proximal tubule, they concluded that the osmotic binding of water by mannitol had prevented its osmotic equilibration while the active transport of sodium continued, but at a moderately reduced rate. This would represent apparent independence of solute and water reabsorption.

The entire argument rests on their assumption that under the conditions of their experiment the distal contribution to sodium reabsorption was not largely in excess of 15%. Homer Smith[33] has marshaled suggestive evidence that in the normal course of events 85% of water is reabsorbed passively in the proximal system and a variable amount up to 15% in the distal system. With regard to sodium, Walker and coworkers[37] concluded from micropuncture studies that 80% of filtered sodium was reabsorbed in the proximal tubule. Under such conditions, the excretion of essentially sodium-free urine would signify that 20% of sodium had been reabsorbed distally. The ceiling for distal reabsorption of sodium is here an artificial one imposed by load limitations. The experimental design of Wesson and associates was such, however, that abnormally large loads were being delivered to the distal segment at a time when it must have been maximally stimulated by the low serum sodium values (approximately 110 mEq./L.) existing at the height of the diuresis. Under such conditions the reabsorptive capacity of the distal system for sodium probably considerably exceeds 15% or 20%.

Are there other means by which the migration of proximal tubular fluid into peritubular capillaries might be effected? Podhradszky[32] showed in 1939 that tubular reabsorption is enhanced by elevating the colloid osmotic pressure of plasma. He found that the sharp reduction of the magnitude of a diuresis induced by infusion of Ringer's solution, when acacia is added, is not accompanied by a fall in filtration rate. Knowlton[19], in 1911, also demonstrated an action of colloids at a tubular level, although he did not so interpret his experiments. This was implicit in his observations that a saline diuresis could be sharply delimited by incorporating gelatin or acacia in the infusion, whereas a sodium sulphate diuresis remained singularly unaffected by the addition of colloids. More recently, Petersdorf and Welt[31] have shown that although an enhanced urinary output of sodium follows infusions of isoncotic plasma, no change, or an actual antinatriuretic effect, follows similar plasma expansions with hyperoncotic solutions. The difficulties in attempting to explain how a rise in the oncotic pressure of plasma could affect an active sodium transport mechanism are well illustrated by the attempts of these authors to formulate a reasonable hypothesis.

An interesting explanation of this phenomenon was advanced in 1947 by

Greiner and Podhradszky[17], who reasoned along the same lines as Carl Ludwig[23] a century earlier. This physiologist proposed what Cushny has termed the "mechanistic theory of urine formation." The following description of this theory is actually an abstract of a later modification in Ludwig's *Lehrbuch der Physiologie des Menschen* in 1861[23]:

Ludwig conceived of filtration and reabsorption taking place in the kidney in much the same way as proposed by Starling for capillary beds in the body at large. The microstructural arrangement of the kidney was, in his view, designed for the purpose of dividing the filtering and reabsorbing capillary beds anatomically so that a membrane barrier in the form of tubular cells could be interposed between glomerular filtrate and peritubular capillary plasma. This tubular wall was conceived of as membrane whose permeability characteristics differed from those of the glomerular membrane. An ultrafiltrate of plasma was said to be formed at the glomerulus in consequence of the fact that the pressure within it, derived from heart's energy, exceeded the fluid-attracting force of blood colloids. Most of this fluid in its course down the tubule was thought to be reabsorbed into the peritubular capillaries in response to the drawing force of colloid osmotic pressure, the remainder being excreted as urine. Alterations in the composition of urine as compared with plasma were explained on the basis of presumably different permeability characteristics for the tubular membrane as compared to the glomerular membrane. Obviously, an over-all reabsorptive process of this nature could not account for the formation of a urine either hypo- or hyperosmolar with respect to plasma. For this reason, even the mechanistically minded Cushny[11] felt obliged to abandon the tubular portion of Ludwig's theory.

One wonders if certain facts brought to light since Cushny's time would have led him to strike less of a compromise with the vitalists and, perhaps, to come to the conclusion that a large portion of tubular reabsorption is a passive consequence of existing oncotic forces. The first of these is the rather formidable fact that in man approximately 180 liters of fluid are filtered daily, 179 of which are reabsorbed. The second is the demonstration by Walker and co-workers[37] that about 80% of this is reabsorbed isosmotically. The third is the porous nature of tubular cells, which has been revealed by electron microscopy[28].

The fact that tubular cells actively transfer substances into and out of the tubular lumen has been proved beyond cavil and, in fact, is implicit in the formation of hypo- or hyperosmolar urines. Without such regulatory mechanisms, molecular constancy could not be preserved in face of the variability of dietary intake. However, their existence does not preclude their superimposition on another, perhaps more primitive, method of tubular reabsorption. It seems feasible to postulate that volume regulation might be subserved by a passive reabsorptive process. Such a process would necessarily have to be flexible in nature, so that at different times the glomerular filtrate would be reabsorbed to a greater or lesser extent. In order that these requirements might be satisfied, in the framework of Ludwig's theory, these reabsorptive changes would have to be accompanied by corresponding changes in the oncotic pressure of fluid entering the peritubular capillary plexus. In particular, two sets of conditions would have to be satisfied: first, those states in which the kidney is acting to conserve volume would have

to be accompanied by an increase in the oncotic pressure of fluid entering the peritubular capillaries; second, those states in which the kidney is acting to reduce volume would have to be characterized by a decrease in the oncotic activity of the plasma flowing into the peritubular plexus. The diuresis induced by administration of Ringer's solution fulfills the second requirement, and the antidiuresis following the rapid administration of concentrated serum albumin into normal individuals[9,31] fulfills the first.

In the edema accumulatory stage of congestive heart failure, however, concentration of plasma protein in the body at large remains unchanged or may even be somewhat decreased. Also, infusion of isoncotic plasma results in diuresis. These phenomena require the presence in the kidney of a mechanism capable of altering the concentration of proteins in plasma leaving the glomerulus. Within the structural make-up of the kidney, there exists a means by which this end can be achieved. The kidney is unique among the organs of the body in possessing two arteriolar resistances placed in series. These contain between them the glomerular bed, in which the hydrostatic pressure can be kept at a high level and at the same time be made to vary, within limits, in face of a constant arterial pressure. If the efferent arteriole constricts, the rate of plasma flow will be slowed, and at the same time intraglomerular pressure will be increased. Consequently, more fluid will be filtered from each unit of plasma flowing through the glomerulus so that the remainder, which leaves to enter the peritubular capillary plexus, will be more concentrated. A dilatation of the efferent arteriole, by causing a reduction of intraglomerular pressure and allowing an increased rate of plasma flow, would have the opposite effect.*

Measurements of this sort can be made in terms of clearance data, in which the degree to which a unit of plasma flowing through the glomerulus is reduced in volume is expressed by the filtration fraction. This, in turn, is defined as the ratio between the rate of glomerular filtration and the rate of renal plasma flow. Inasmuch as this represents an average of the filtration

*These relationships may be expressed mathematically, in terms of glomerular filtration rate and renal plasma flow, as follows:

$$P_e = P_a \left(\frac{1}{1 - FF} \right) \text{ where}$$

P_e = protein concentration of fluid leaving the efferent arteriole.
P_a = protein concentration of the fluid entering the afferent arteriole.

$$FF = \text{filtration fraction} = \frac{GFR}{RPF}$$

GFR = rate of glomeruar filtration
RPF = rate of plasma flow through the nephrons

Example calculations for a plasma protein value of 6.0 gm. per 100 ml. at two different filtration fractions is given below:

$$\text{at an FF of 0.2, } P_e = 6.0 \left(\frac{1}{1 - 0.2} \right) = 7.5 \text{ gm. per 100 ml.}$$

$$\text{at an FF of 0.4, } P_e = 6.0 \left(\frac{1}{1 - 0.4} \right) = 10.0 \text{ gm. per 100 ml.}$$

fractions of all nephrons receiving blood, it would be valid for our purposes only if the deviations from the mean in individual nephrons were not excessive.°° This requirement is probably not fulfilled under conditions of shock or when renal disease is present. For this reason, we will confine ourselves to examination of clearance data obtained in normal individuals or to those studies in which an effort was made to exclude patients with renal disease. Under this theory, the following conditions must be fulfilled: First, in conditions of circulatory excess, in which volume is being contracted by increased urinary excretion of salt and water, the filtration fraction should be low. Second, in conditions of circulatory inadequacy, wherein volume tends to become expanded by decreased urinary output of water and salt, the filtration fraction should be high.

Wilson and Harrison[41] observed the effects of administering about one liter of plasma to each of 8 convalescent male patients. There was without exception a fall in filtration fraction from an average value of 0.28 before infusion to an average value of 0.20 after infusion. Save for one exception, there was a concomitant sharp increase in urinary outflow. Since exogenous creatinine clearance was used as a measure of filtration rate, the absolute values of filtration fractions are erroneously high, but the directional changes remain valid. Using inulin clearance as a measure of glomerular filtration rate and correcting renal plasma flows with observed PAH extraction fractions, Cargill[9] reported a fall in filtration fraction in each of 3 normal individuals following expansion of plasma volumes. This was achieved by administering 75 gm. of serum albumin in the form of a 25% solution. Since in this instance, as theory would predict, the fall in filtration fraction was nullified by a concomitant rise in serum oncotic pressure, no significant change in urinary flow was observed. Similar results with regard to filtration fraction were obtained by Bradley and co-workers[5] with slow infusion of 50 gm. of serum albumin. In this instance, because of the slow rate of administration, the plasma protein level was probably not significantly elevated, and increased urinary flows were observed. On the other hand, Fleming, Cargill and Bloom[16], using dextran as a plasma expander, observed no significant change of filtration fraction. The applicability of these latter results to the present problem is beclouded because of possible differences in the permeability of the glomerular membrane towards dextran and plasma protein.

Congestive heart failure is an ideal example of a condition wherein circulatory inadequacy may exist with a tendency to volume expansion. The studies of Heller and Jacobson[18] are particularly instructive in this regard. They performed clearance studies on patients with valvular heart disease selected to avoid complicating renal dis-

°°Wide deviations of filtration fractions from the mean value on the low side may be caused by an abnormally low rate of glomerular filtration. This could result from an abnormally low intraglomerular pressure or actual reduction of glomerular surface area, as occurs in disease. Under these conditions, a low filtration fraction would result in low urinary flow rates instead of the high rates predicted by theory. If a sufficient number of such nephrons were present, the over-all average for filtration fraction could be normal or even low in spite of the fact that the remaining intact nephrons might possess high filtration fractions. This may be the state of affairs in the edema accumulating stage of nephrosis, in which theory would predict a high filtration fraction but reported clearance values range widely, tending to be normal or low[7]. A somewhat similar situation may prevail in the condition of shock, in which low filtration fractions have been reported[20].

case. These patients were divided into three groups: Group A consisted of patients with rheumatic valvular heart disease but without previous or present evidence of congestive heart failure. The filtration fraction in these patients averaged 0.23. Group B consisted of patients with congestive heart failure at the time of admission to the hospital but who were clinically compensated at the time of the study. The average filtration fraction in this group was 0.28. Group C was composed of patients in whom signs of cardiac decompensation were present at the time of the determinations of renal hemodynamics. Their mean filtration fraction was 0.41. In a series of normal control subjects, the mean filtration fraction was 0.17. In individual patients studied serially while they were edematous and later when they became edema-free, a fall in filtration fraction was consistently observed. Whereas, on the whole, other clearance studies on congestive heart failure agree closely with these results[25,27], occasional discrepancies have been reported in which the height of the filtration fraction did not reflect the severity of the clinical picture of failure. These may have been due to the presence of renal disease or congestive heart failure of such severity that a circulatory state akin to shock existed.

Thompson and Pitts[36] report tubular reabsorption of sodium to be increased following inflation of a balloon in the aorta of dogs proximal to the origin of the renal arteries. Calculation of filtration fractions from their data reveals that in many instances this was not accompanied by an increase in FF. Fitzhugh and associates[15], on the other hand, found the decreased urinary output of sodium and water induced by trapping of blood in the lower extremities by tourniquets to be consistently associated with increased filtration fractions.

These collective data, although not conclusive, support the fact that circulatory inadequacy is accompanied by high filtration fractions and circulatory excess by low filtration fractions, thereby fulfilling the criteria necessary for a volume regulation based on passive reabsorption of tubular fluid in response to oncotic forces existing in the peritubular capillaries.

This would by no means preclude the simultaneous operation of active transport mechanisms such as have been demonstrated for reabsorption of glucose in the proximal tubule. Furthermore, if frictional losses were neglected, the energy conferred on plasma leaving the glomerulus, in the form of increased colloid osmotic pressure, would be, theoretically, capable of causing reabsorption of all the filtrate. Therefore, certain factors, such as time, surface area, and the presence of substances to which the glomerular membrane is freely permeable but to which the tubular membrane is relatively impermeable, presumably militate against complete oncotic equilibration. The degree to which this proceeds is related to the intensity of the oncotic forces involved.

Plasma volume is, then, conceived to occupy an intermediate position with respect to the interstitial fluid on one hand and the kidney on the other. Its volume is maintained by balances achieved between the rates of filtration and reabsorption governed by hydrostatic and oncotic forces, as described for the capillary interface at large by Starling and for the kidney by Ludwig. In terms of a crude analogy, the kidney functions as an overflow valve in this system.

If, indeed, it is true that volume regulation is achieved in such a mechanical way, the question might be

properly raised as to why the kidney would use such a circuitous route requiring the filtration and reabsorption of large quantities of fluid, since the same result could be achieved more economically at a glomerular level. However, one important advantage is gained. If, due to blood loss, the need to conserve fluid arises, a shutdown at the glomerular level would result in failure to excrete such filtered metabolic end products as creatinine and urea. On the other hand, the more extravagant process would permit excretion of these products because of their limited diffusability through the tubular membrane, while the necessary water and salts could be reabsorbed.

The ability of the kidney to alter efferent arteriolar resistance in a manner to permit attainment of appropriate intraglomerular pressures remains unexplained. This apparently autonomous ability has been ably discussed by Smith[33] and Winton[40]. That this mechanism does not respond to cardiac output can be deduced from the fact that a tendency toward volume expansion exists in states characterized by both low and high rates of blood flow. Borst[4] has introduced the terms "inadequate circulation" and "excessive circulation" to express, respectively, blood flows insufficient and excessive with relation to the needs of the organism. He conceived of these as the ultimate stimulus. Peters[30] gave more precise expression to this when he ascribed the diuretic response to the fullness of the arterial stream. The volume of blood contained within the arterial tree is governed by a dynamic balance between inflow and outflow. When this balance is upset in a direction to increase the volume contained within the arterial tree, filtration fraction probably falls and a diuresis occurs. When, on the other hand, an imbalance results in a fall in volume of blood within the arterial segment, filtration fraction rises and an oliguric response is seen.

In summary, it may be said that the final composition and amount of urine reflect the contribution of many complex operations subserving a number of different needs, one of which is volume regulation. The participation of the kidney in the preservation of a constant ECF volume has been reviewed as follows.

The unique nature of volume regulation has been defined, and evidence has been cited to suggest that the renal mechanisms concerned with its control are separate from, and may act independently of, those concerned with the regulation of molecular pattern of ECF. The current trend is to think of renal volume regulating mechanisms in terms of active transport systems for the predominant extracellular ions. Some of the difficulties associated with any attempt to define or locate proper receptor and transmitter mechanisms necessary for the control of active transport systems have been presented. Lack of convincing evidence for an active sodium transport mechanism located in the proximal segment of the tubule has been discussed.

An alternative view has been advocated that related volume regulation with hemodynamic and physical alterations of renal function. Evidence has been cited suggesting that the final common pathway in this process is related to the oncotic pressure of plasma entering the peritubular capillaries. This oncotic pressure has, in turn, been shown to be related to filtration fraction, which becomes smaller or larger, depending on the adequacy of the circulation in the body as a whole. If permeability characteristics for the wall of the proximal segment of the tubule are assumed to permit free diffusion of water and the principal electrolytes of glomerular filtrate, the isosmotic com-

ponent of tubular reabsorption would be regulated by the intensity of the oncotic forces exerted by the peritubular plasma proteins. Variations in reabsorption of tubular fluid brought about in this manner could constitute a mechanism for volume regulation. In order to define this servomechanism completely, the link between circulatory changes in the body at large and hemodynamic alterations in the kidney must be explained. This problem of autoregulation has as yet defied analysis.

For those who may feel that bias has been displayed in favor of a somewhat mechanical interpretation of volume regulation, it may be pertinent to recall the situation existing in renal physiology at the turn of the century. At this time the Bowman-Heidenhain school advocated the vitalistic view that the formation of urine consisted in an active secretion by the glomerulus of a fluid to which urinary solutes were added by active tubular secretion. The comment on this theory by Cushny[11], who advocated a more mechanical interpretation is of interest and may perhaps be invoked in defense of the position taken here:

"It has the advantage that no possible conjunction of conditions can be imagined which cannot be attributed to some special activity of unspecified cells, whose activity is governed by no known laws and whose anatomical position in the organ can be arranged to suit the circumstances. But such a nebulous statement of the renal function, while it offers a facile explanation of all observations, in reality explains nothing. As a defensive position it is impregnable, but it offers no point from which advance may be made. It may be necessary to retreat to it as a base if more adventurous theories are overthrown, but it would merely be a temporary position to be occupied until a more successful effort could be made to coordinate our knowledge of the activity of the kidney."

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SUMMARIO IN INTERLINGUA

(See page 76 for original article)

Apparentia de Defecto Renal in Individuos Drepanocytemic

1. Studios de function renal esseva executate in 16 patientes con anemia a cellulas falciforme, 33 con tracto de cellulas falciforme, 2 con tracto combinate de cellulas falciforme e thalassemia, e 1 con tracto combinate de cellulas falciforme e hemoglobina C.

2. In omne gruppos le valores median del tests clinic de function renal esseva ben intra le limites normal.

3. Le plus frappante constatation esseva le restringite capacitate de excerner urina concentrate post abstention ab fluidos durante 18 horas.

4. Iste defecto esseva plus pronunciate in individuos con anemia a cellulas falciforme que in individuos con tracto de cellulas falciforme. In le prime de iste duo gruppos le maximo median del pression osmotic del urina esseva 421 mOsm per litro. In le secunde gruppo le correspondente valor esseva 604 mOsm.

5. Es presentate rationes pro considerar le lesion como renal, de natura physiologic o metabolic, e hereditabile como parte del stato drepanocytemic.

NEUROLOGY AND PSYCHIATRY

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TENSION HEADACHE: A REVIEW

BY FRANK R. DRAKE, M.D.

TENSION headache is undoubtedly the most common variety of headache as well as the commonest complaint of patients in the office practice of general medicine. It occurs in relation to constant or periodic emotional conflict which may be conscious or unconscious[23,25,32]. Tension headaches have no prodromata, are usually bilateral, occipital, or frontal, and may be accompanied by anxiety (free-floating or somatized) and such symptoms as nausea and vomiting, dizziness, weakness, irritability, and constipation[12,16,27,31,49,57,59,73,74,76]. The frequency and duration are variable, but an attack may last for weeks[48,50]. The discomfort has been described by various authors as "constant, and boring, unlike the throbbing quality of the migraine headache"[41]; "bizarre, rarely interfering with sleep, a tight feeling as of a band around the head"[16], "vague and dull, or a sensation of pressure in the head" [39,49]; "a dull aching tenseness in the neck"[54]; "head caught in a vise, or scalp on too tight, or top of my head blowing off"[36]; "tends to be worse toward evening when the patient is nervous or tired"[64]; "the pain begins in the occipital zone, extends into the forehead and may center there or in the vertex"[75]; and "poorly defined, with a complete lack of any features characterizing them as another type of headache"[10]. The patient tends to have a worried and unhappy facial expression but otherwise may present the picture of robust health.

Other Common Headaches. 1. CONVERSION (HYSTERICAL) HEADACHES. These headaches are often almost indistinguishable clinically from tension headaches. The main distinction is that in conversion headache the symptoms represent a specific unconscious symbolic meaning and the conversion mechanisms are prevalent. The typical "la belle indifference" of hysteria may or may not be apparent. Appropriate psychological tests may shed much light on the matter. Wolff[78] states that these patients "use the word pain to describe sensations resulting from the effects of non-noxious stimulation because past conditioning experiences have modified their interpretation of any head sensation. As a result, non-painful sensations from the head have assumed special significance for such individuals, mak-

ing them, in view of their preoccupations and misevaluation of head sensations, untrustworthy witnesses of head pain. Distortions of judgment in such persons may be shown in the misevaluation not only of the pain threshold but also of the intensity of head pain. Furthermore, these persons may show defects in other sensory discrimination, should these happen to involve symbols significant to the given individual."

2. MIGRAINE HEADACHES. The following comparison of the characteristics of 1000 cases of migraine and a similar number of cases of tension headache is worthy of quotation[35]:

		Percent	
		Migraine	*Tension*
"Family history of headache		65	40
Age of onset	less than 20 years	55	30
	over 20 years	45	70
Prodroma		60	10
Frequency	constant or daily	3	50
	less than 1/week	60	15
Duration	constant or daily	0	20
	1 to 3 days	35	10
Type, throbbing		80	30
Location	unilateral	80	10
	bilateral	20	90
Associated symptoms, vomiting		50	10

Migraine and tension headaches did not differ significantly in respect to the following: incidence, sex, precipitating causes, occurrence (time of day or season), mood change, onset, and termination (abrupt or gradual)."

3. HISTAMINIC CEPHALAGIA. This syndrome was first described by Horton[44, 45, 65]. It is a unilateral vascular headache which usually begins in the later decades of life. It begins and ends suddenly and generally lasts less than an hour. "It tends to awaken the patient at night one or two hours after he has gone to sleep, and the severity of the pain makes the patient get out of bed and pace the floor. At its height the pain is associated with watering and congestion of the eye, rhinorrhea or stuffiness of the nostril, sweating, and often, visible dilation of the temporal vessels of the involved side of the head. Constant, excruciating, burning, and boring pain is the outstanding complaint. It involves the orbital area and the temple and may extend to the upper jaw, occipital region, neck, and shoulder. Severe and frequent attacks of pain may occur as often as 20 times or more a week. The attacks are usually not accompanied by gastrointestinal symptoms or visual disturbances. About 90% of the patients are men over 40 years of age. Approximately 40% of patients have observed that alcohol will precipitate attacks"[43]. In regard to this type of headache, another viewpoint should be presented: "We believe that this syndrome exists. Many neurologists doubt its existence, believing it to be due to some organic factor such as aneurysm of cerebral vessels. Their arguments are well taken, and the basis of such a condition is not firmly established"[16].

Physiology. In tension headaches a muscular or vascular mechanism may act independently or concomitantly. The tense, apprehensive, or anxious patient seems to be constantly poised to go into action[77]. The persistent tension causes a sustained contraction of the skeletal muscles of the head and neck, with resulting pain. Associated with these muscular spasms may be ischemia, which could be a contributory or primary factor in the production of pain. One theory is that excessive concentration of potassium in muscle, due to ischemia or sustained contraction, stimulates the chemoreceptors in the tissues. There also may be a central spread of the excitatory effect of noxious stimulation of the soft tissues of the neck. This spread of pain would then be carried by the upper cervical nerves and produce painful sensations

in the forehead and face[25]. There are some who believe that tension headache is at least partially due to painful vasodilatation which follows an early vasoconstriction[16,39].

Psychological Causes. In most cases of tension headache the precipitating psychic factors are largely unconscious. However, many patients are aware of the associated anxiety. Environmental demands of an intellectual, physical, social or economic nature beyond the capacity of the patient's personality may also produce headache. Emotional conflicts concerned with hostile impulses toward loved ones or associates are usually present. Many patients develop the headache when they reach the limit of their capacity to tolerate their repressed or suppressed anger and resentment. Unconscious or conscious guilt practically always accompanies the hostile impulses. Other factors which may play a role in the head pain are identification with a family figure who may also have headaches, the wish to remain in a position of dependency, and a desire to gain attention.

Combined Headaches. Tension headache often appears in combination with migraine headaches when the migrainous individual is under prolonged stress associated with a fatigue state. Such a headache is called "Migraine-tension" headache, a variety which lies between the extremes of typical migraine and typical tension headache[2,38,47,64,68]. Many patients with migraine, if not adequately treated for days, will develop sustained muscle tension in the head and neck with additional headache. Any one patient may, at different times, develop either type of headache, each of different severity and duration and each requiring different treatment[5,33,36]. Some physicans believe that a true breakdown of most cases of migraine would be found to consist of a combination of migraine and tension[68].

Treatment of Tension Headaches. 1. PSYCHOTHERAPY. The most important single factor in the psychotherapeutic process is the emotional relationship between the patient and the physician. When the patient feels that the physician is sincerely interested and sympathetic, he will then permit the tactful exploration of those factors in his life situation which have led to resentment, hostility, guilt, and the like. The aeration and ventilation of wholly or partly unconscious emotional conflicts are important. The physician must learn to listen patiently. Simple explanation of the effect of the emotions on bodily functions may be helpful. Reassurance, suggestion and re-education are other techniques which may help the patient to gain the necessary security and readjustment to life. Such treatment is well within the province of the interested general practitioner[17,32]. Sometimes tension headaches seem to be relieved for variable periods of time by nothing more than the establishment of excellent rapport with the patient, the so-called "transference cure"[26,28,70].

2. ENVIRONMENTAL MANIPULATION. This procedure consists in helping the patient to so alter stressful situations in his work, recreation, family or social life that he will not exceed his emotional capacity. A sustained hobby may be beneficial in securing relief from the stresses of daily living[32,33].

3. PHARMACOTHERAPY. The efficiency of medication does not depend entirely on its pharmacologic action. The importance of dosage, timing, and mode of administration cannot be overstressed. It also depends upon the authoritative effect of the physician prescribing the medication as well as the length and frequency of concurrent interviews with the patient[27]. Strong suggestion from a respected physician

as to the therapeutic benefits to be expected from any particular drug is notoriously effective in the therapy of tension headaches. The following drugs are valuable adjuncts to the psychotherapeutic treatment of tension headaches:

a) Acetylsalicylic acid or Bufferin, in doses of 0.3 to 0.6 gm. (5 to 10 gr.) and repeated if necessary in one or two hours will often give symptomatic relief and make psychotherapy easier[19]. It should be kept in mind that hypersensitivity to acetylsalicylic acid is not uncommon, and that the mechanism is probably that of allergy. "This supposition is indicated by the capacity of acetylsalicylic acid to attach itself to proteins and thus become antigenic, as demonstrated by the experimental production of anaphylactic shock and positive skin reactions. Moreover, the systemic clinical expression of hypersensitivity is bronchial asthma, which is usually identified with this mechanism. Walton and Bottomley found acetylsalicylic acid sensitivity in 2.6% of 830 successive hospital admissions"[1,21,22].

b) Fiorinal (Sandoz) is one of the best sedative-analgesic preparations for the temporary treatment of tension headache[13,31,35,49,76]. Each tablet consists of 0.05 gm. (3/4 gr.) of isobutylallylbarbituric acid, 0.13 gm. (2 gr.) acetophenetidin, 0.2 gm. (3 gr.) of acetylsalicylic acid, and 0.04 gm. (2/3 gr.) of caffeine. When taken in a dosage of one or two tablets every four hours, Fiorinal tends to prevent a mounting build-up of nervous tension, and, in addition, seems to relax the musculature about the head and neck. Easing of the head discomfort is generally accomplished without any unpleasant side effects such as gastric upset[49]. Since Fiorinal has a barbiturate component it is contraindicated for prolonged use in uncomplicated tension headaches and should be restricted, in general, to the following: The early stages of psychotherapy, before the psychotherapeutic process and environmental manipulation have had an opportunity to help reduce the tension; those cases of tension headache which occur infrequently and only under unusual and temporary stress in stable individuals; those cases of tension headache which occur in patients who are resistant to psychotherapy or whose environment cannot successfully be manipulated, or both.

c) Miltown (Wallace) and *Equanil* (Wyeth), meprobamate-(2-methyl-2-n-propyl-1, 3-propanediol dicarbamate). These identical tranquilizers[9,14,51,71] are often effective in the treatment of mild and moderate tension headaches. Either drug may be administered to adults in an initial dose of one tablet (400 mg.) orally three or four times daily. When a satisfactory diminution in symptomatology has occurred, the dosage is reduced to one-half of a tablet three or four times daily. No serious side effects have been reported from the use of Miltown or Equanil. An occasional patient will complain of drowsiness, which, however, usually disappears on reduction of the dosage. They are apparently non-habit forming and without known contraindications.

d) Valoctin (Bilhuber-Knoll), 5 gr. tablets, each containing 1 gr. (60 mg.) of "Octin" (methylisooctenylamine) and 4 gr. (250 mg.) of the non-barbiturate sedative "Bromural" (monobromisovalerylcarbamide). It is administered orally, in a dosage of one or two tablets at the onset of the headache, and is often effective in ordinary tension headaches as well as those with a small throbbing (vascular) component. One additional tablet may be prescribed after 4 hours if necessary. The "Octin" in Valoctin causes mild vasoconstriction of carotid and cerebral vessels. The "Bromural" in Valoctin is, of course, a

well known daytime sedative and diminishes the tension which causes the muscle spasm of tension headaches[68].

e) Octin (Bilhuber-Knoll), methylisooctenylamine, has been used for a number of years in the treatment of vascular headache when ergot is contraindicated[34,42,63,64,66,68]. It is not as vasoconstrictive as ergotamine preparations, but, because of its antispasmodic properties, is often administered in vascular headaches (associated with severe gastrointestinal disturbances). Because of its moderate hypertensive effect it cannot be given intravenously or used in cases of hypertension. Hypertension is the sole major contraindication to the use of Octin. Since many tension headaches seem to have an associated throbbing or vascular "contamination," it is often desirable to try this relatively harmless moderate vasoconstrictor before resorting to the more powerful, more effective, and more side-effect-producing ergotamine preparations. For this purpose one tablet of Octin Mucate (2 gr.) may be administered orally every 30 minutes, up to four tablets, until relief is obtained. If Octin Mucate is not effective, 1 ml. (1½ gr.) of Octin hydrochloride may be injected intramuscularly.

f) Reserpine. Almost any of the proprietary brands of reserpine, in oral doses of 0.25 to 0.75 mg. daily may at times reduce or abolish tension headaches. This is because of its well-established tranquilizing effect on anxiety and tension states. However, one should be aware of the fact that depression may result from the use of this drug in susceptible individuals. In addition, one should not expect an immediate reduction in tension with oral reserpine as several days are usually required for maximum therapeutic effect. Parenteral reserpine is ordinarily not considered indicated in the therapy of the uncomplicated cases of tension headache which one sees in office practice[20,23,24].

g) Thorazine (Smith, Kline &, French), chlorpromazine hydrochloride. Oral Thorazine may reduce or abolish tension headaches within a few days following its initial administration. It is administered to adults initially in a dose of 10 mg. after each meal, in mild to moderate tension states, and is gradually increased to a total of 100 mg. daily over a period of a week or so. Hypotension, depression, dermatitis, and jaundice are the most distressing possible side effects. It is well not to use parenteral Thorazine in the therapy of outpatients suffering from uncomplicated mild to moderate tension headaches because of the possible hypotensive effect as well as the inconvenience of frequent injections[7,11,61].

h) Ergotamine Preparations. Although ergotamine preparations are primarily indicated in "pure" vascular headaches such as migraine[56], they are also useful in those "impure" combinations of muscle spasm and vascular headaches which are not completely responsive to the usual therapy for tension headaches. Contraindications to the use of any of the ergotamine preparations include peripheral vascular disease, coronary heart disease, hypertension, impaired renal or hepatic function, pregnancy, sepsis, toxemia, and malnutrition[11,27,34,37,64]. They should be tried in the following order until the most simply and conveniently administered preparation has been found to be effective:

(1) *Cafergot tablets* (Sandoz), each containing 1.0 mg. of ergotamine tartrate and 100 mg. of caffeine. The patient is instructed to take two tablets orally at the onset of an attack. If necessary, one additional tablet may be taken every 30 minutes to a maximum total of six tablets in any one day[58].

(2) *Cafergot-PB suppositories* (Sandoz), containing 2.0 mg. of ergotamine tartrate, 100 mg. of caffeine, 0.25 mg. of Bellafoline, and 60 mg. of pentobarbital sodium. One suppository may be administered at the onset of the attack and a second one after one hour if necessary. The usual precautions against the sustained use of barbiturates should be realized and observed when prescribing this excellent suppository. The Bellafoline in each suppository is anticholinergic and antiemetic in effect[11,18,27,55,8,64,67,68,69].

(3) *Dihydroergotamine* (Sandoz) also known as D.H.E.–45. It is dihydroergotamine methanesulfonate, a crystalline alkaloid produced by hydrogenation of ergotamine. D.H.E.–45 is less likely to produce nausea and other side effects than the older ergotamine tartrate (Gynergen) and will generally relieve the throbbing vascular component of a combined migraine and tension headache by checking the cranial vasodilatation involved. One milliliter of D.H.E.–45 (1 ml. equals 1.0 mg.) is administered intramuscularly shortly after the first warning of a migraine-tension headache. If relief of the throbbing vascular component of the headache is incomplete after an hour, the same dose may be repeated[3,11,34,46,64].

Parenteral ergotamine preparations should not normally be utilized more than twice weekly as there is increasing evidence that more frequent use may result in an increased frequency of headaches, possibly due to the fact that "Ergotamine may sensitize cranial arteries and increase their susceptibility to stimuli which would produce vasodilatation. These possibilities may be independent of tolerance and addiction or may be part of such phenomena." Then, too, their discontinuance may be followed by daily "withdrawal" type headaches for a week or more[8,29,52,65]. In addition, the following symptoms of ergotism may accompany their over-use: coronary spasm due to the constrictor effect on coronary vessels; muscular cramps in neck and extremities; numbness, cyanosis, and paresthesias of the extremities[29,65].

General Considerations. 1. In the diagnosis of tension headache the taking of a thorough and detailed history is of first importance. However, a complete general physical and neurological examination not only increases the diagnostic accuracy but also helps to instill confidence in the physician. The following studies may be done as indicated: Complete blood count, urinalysis, blood serology, visual fields, special examinations of the eyes, ears, nose and throat, roentgenograms of the head and cervical spine, spinal fluid examination, basal metabolism, electroencephalogram, and pneumoencephalogram[10,62,64].

2. Tension headache has a more specific etiology than migraine but is not as precisely defined clinically or physiologically[27]. The manifestations of migraine have been fairly well systematized since the time of Galen[15].

3. The role of tension is significant in the vast majority of headaches, regardless if it alone causes the headache or if it merely precipitates or enhances an actual specific type of migraine, histaminic, hypertensive, or other type of headache[13,16].

4. Tension headaches may not only occur in combination with migraine but also with such conditions as hypertension and arthritis of the neck[4].

5. The vast aggregation of chronic headaches are, in practice, very difficult to separate into specific single types[72].

6. The character of a headache is usually helpful but is often misleading. Pain described in a wealth of metaphor and by a lavish use of superla-

tives is not necessarily psychogenic but may well be organic in origin. Vertigo may be a premonitory sign of a migraine headache, but it may also be associated with headaches due to head trauma, brain tumor, or emotional tension[33].

7. Sustained muscle contraction in the neck and scalp are not always psychogenic in origin, as local cervical pathology or even generalized infections may be the underlying factor[33].

8. Recent reports tend to minimize the association of headache with eye strain, constipation, and chronic sinusitis[28,33,60].

9. Medication for the symptomatic relief of headache should not ordinarily be prescribed without concomitantly helping the patient to modify the conditions of overwork, fatigue, and other strains that have caused the tension headache to develop[13,19].

10. The treatment of choice in tension headache is a combination of psychotherapy and drug therapy[35].

11. Psychotherapy is a more effective prophylactic measure than pharmacotherapy[31].

12. The number of therapeutic agents recommended for the treatment of tension headache indicates the unsatisfactory status of drug therapy alone for this condition[6,28,52].

13. Almost equally good results in the treatment of tension headaches have been obtained by the use of placebos as by the use of more "specific" medications[27,30].

14. Narcotics and barbiturates should not ordinarily be used for the treatment of tension headaches because of the grave danger of addiction[40,53].

15. If one overlooks or fails to treat the psychological conflicts in chronic headaches of psychogenic origin, he runs the risk of therapeutic failure[30].

16. Personality studies can be very helpful in the study of a patient with headache. However, it does not necessarily follow that the personality problems discovered are the sole or even predominant cause of a particular headache[33].

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MARCH 20, 1956

INFORMAL SEMINAR ON AUTONOMIC GANGLIA

Foundations for Ganglionic Blocking Agents. SYDNEY ELLIS, PH.D. (Department of Pharmacology, Temple University School of Medicine). The concept of chemical blockade of synapses, including those in autonomic ganglia, was introduced by Langley (1889) with his classic use of nicotine. Nicotine still maintains its position as a useful experimental tool, but only for laboratory use. Selective ganglionic blockade was accomplished when Burn and Dale (1915) discovered that the tetraethylammonium ion (TEA), which elicited no nicotine-like stimulating action at autonomic ganglia, antagonized the ganglionic stimulating action of the tetramethylammonium ion. This important discovery lay relatively dormant until interest was aroused in TEA because of its veratrine-like effect on nerve and its cardiovascular effects in anesthetized animals which resembled the Bezold-Jarisch reflex response of the veratrum alkaloids. In detailed investigations Acheson and Moe (1945, 1946) established the site and mode of action of TEA at ganglia. Clinical applications were found in spite of several practical deficiencies of TEA. With the introduction of hexamethonium (Paton, Ing) a more potent, longer-lasting therapeutic agent with some oral activity was available. Hexamethonium remains the prototype for most of the newer ganglionic blocking agents, but the search continues for agents with good absorption when taken by mouth and with dependable action of long duration. It is a moot question whether there can be found agents of this type which will produce only selective, desirable effects without the additional undesirable effects which seem inherent in agents which suppress ganglionic transmission.

Functional Organization of the Peripheral Sympathetic System. JOHN DEMPSHER, M.D. and WILLIAM K. RIKER, M.D. (Department of Pharmacology, University of Pennsylvania School of Medicine). A major function of the peripheral sympathetic system is to integrate a variety of actions which go on simultaneously. Anatomically, the peripheral sympathetic system is organized for such integrative action at the level of the peripheral ganglia. The most likely site is at terminal portions of the presynaptic nerve. Studies have revealed that one presynaptic neuron can terminate, by virtue of its many endings, upon as many as thirty postsynaptic neurons. Furthermore, one postsynaptic neuron receives endings from more than one presynaptic neuron. In addition, some histologists have described connections between postsynaptic neurons. Thus, anatomically, there are two possibilities for spread or integration among the neurons in the ganglia.

The use of electrical instruments for functional studies reveals that the integration is not at the postsynaptic level. For example, the responses, obtained from one postsynaptic nerve of the su-

perior cervical ganglion while stimulating another postsynaptic nerve, are abolished by removing the influence of the presynaptic nerve terminations. This is done either by the removal of calcium from the environment, or by chronic section of the preganglionic nerve. Thus the integration is at the presynaptic level. Additional evidence for this is as follows: superior cervical ganglia rendered hyperexcitable by a virus have spontaneous bursts of impulses discharged over both nerves only when the presynaptic nerve terminations are intact.

The role of acetylcholine in the integration at synapses was examined in the virus-infected ganglia. The interpretation was made more simple by examining ganglia in which the postsynaptic neurons were rendered completely inexcitable. Thus one virtually had a preparation consisting only of a presynaptic axon with its terminal filaments. Acetylcholine applied to such a preparation increased the presynaptic spontaneous activity as did applied eserine. Applied curare depressed the activity. Thus, since applied acetylcholine and eserine increase the spontaneous activity, and curare depressed the activity originating in the presynaptic terminations, the suggestion is made that acetylcholine may play a role in the spread or integration of impulses in sympathetic ganglia.

The Pharmacology of Autonomic Ganglionic Blockade. ALBERT J. PLUMMER, PH.D., M.D., (Research Department, Ciba Pharmaceutical Products, Inc., Summit, New Jersey). Autonomic ganglia consist of groupings of preganglionic neurons whose axons are in close contiguity across a synapse with the dendrites of postganglionic neurons. Ganglia may be considered as switch points or relay centers at which efferent nerve impulses are distributed and transferred over multiple postganglionic pathways on their peripheral course. Despite marked anatomic differences between the ganglia of the sympathetic and parasympathetic divisions, it appears that there is a common mechanism of impulse transmission across the synapses which is due to the depolarizing action of acetylcholine liberated at preganglionic nerve terminations.

In general, therefore, ganglionic blocking agents which impede the passage of impulses through autonomic ganglia affect both divisions. These substances may be classified on the basis of mechanism and specificity of effect. One group of compounds, typified by tetraethylammonium and hexamethonium chloride appears competitively to interfere with the depolarizing effect of acetylcholine on the postganglionic neuron by virtue of close chemical structural similarity to this ganglionic mediator. A second type of blockade is produced by nicotine which directly depolarizes the postganglionic neurons, thus causing initially a ganglionic stimulation which is ultimately transformed to depression and blockade because of persistent depolarization. Still a third mode of ganglionic inhibition is exemplified by the cholinesterase inhibitors which permit the accumulation of acetylcholine within the ganglia, thus bringing about a persistent depolarization of the ganglion. Finally, a miscellaneous group of substances including anticholinergic, antihistaminic, local anesthetic and hypnotic agents interfere with ganglionic transmission. The primary pharmacological actions of these substances are *prima facie* evidence of their lack of specific ganglionic effect.

The designation "ganglionic blocking agent" is generally understood to include only those compounds of the first group which compete with acetylcholine; this group has a high specificity

of effect, as the action of acetylcholine at other than ganglionic sites is not hindered.

The primary result of specific blockade is a reduction in autonomic tone to the smooth muscle of the blood vessels and viscera, to the heart, and to the secretory glands supplied by this system. Major interest has been directed toward the hypotensive action resulting from decreased sympathetic vasoconstrictor tone.

A discussion of factors influencing potency, duration of action, oral effectiveness and general pharmacological characteristics will be based primarily upon a comparison of the hexamethonium and chlorisondamine chloride series of blocking agents.

Pharmacology and Physiological Disposition of 3-methylaminoisocamphane (Mecamylamine): A Secondary Amine Ganglionic Blocking Agent. CLEMENT A. STONE, PH.D., JOHN E. BAER, PH.D., EUGENE J. ZAWOISKI, M.A., and KARL H. BEYER, M.D. (The Merck Institute for Therapeutic Research, West Point, Pa.) The ganglionic blocking activity of 3-methylaminoisocamphane (mecamylamine, Inversine) was revealed by a capacity to inhibit the vascular responses to peripheral vagal stimulation, carotid occlusion and injected nicotine in the dog in intravenous doses of 0.1 mg./kg. or greater. In addition, contractions of the nictitating membrane, elicited by preganglionic nerve stimulation in cats, also were inhibited. Since epinephrine or acetylcholine vascular effects in the dog, or epinephrine-induced membrane contractions in cats, were not blocked, a ganglionic blocking effect was indicated. In terms of potency, mecamylamine was equiactive with pentolinium in blocking nicotine pressor responses in cats and some two to four times more active than hexamethonium, but the effects of mecamylamine endured three to five times longer than either. That the compound was well absorbed after oral administration was reflected in the small ratio between oral to intravenous equiactive doses in dilating the pupils of mice, as compared to similar ratios obtained with quaternary ammonium blocking agents. The ratios of these latter agents were ten to twenty times larger than the corresponding ratio for mecamylamine and indicated that the secondary amine was much better absorbed. Renal clearance of mecamylamine in the dog exceeded that of creatinine whenever the urine was acid and was less than creatinine when the urine was alkaline. The clearance of mecamylamine was increased by the administration of ammonium chloride, or depressed by sodium bicarbonate or acetazoleamide. The compound was found to be concentrated in the gastric juice of Heidenhain-pouch dog 20 to 40 times the concentration in plasma whenever the gastric secretion was highly acid, as after the choline or sodium acetate. This latter effect, by a cyclization process, may contribute to the demonstrated long duration of action of mecamylamine.

BOOK REVIEWS AND NOTICES

ENDOTHELIUM. ITS DEVELOPMENT, MORPHOLOGY, FUNCTION, AND PATHOLOGY. BY RUDOLF ALTSCHUL, M.U.DR., Professor of Histology, University of Saskatchewan. Pp. 157; 9 ills. New York: The Macmillan Company, 1954. Price, $3.50.

THERE has been a considerable tendency in recent years to focus interest on general metabolic processes in connection with the etiology of degenerative vascular disease. This focus, however, has not detracted from the very strong possibility that injury of the vascular endothelium may be a very important factor. The endothelium is the chief element of any vessel, and in those conveying blood is under almost constant mechanical and functional stress, yet is not readily replaced. Unlike epithelium, this vascular lining cannot respond with proliferation to pressure stresses without interfering with its function of nutritive exchange. The wonder is, as Dr. Altschul points out, that atherosclerosis is not even more common.

The present volume brings together in a scholarly manner all information pertaining to endothelium available to the author from over 400 domestic and foreign sources, and an attempt has been made by him to correlate this as well as can be done in the present state of knowledge. Unhappily the reader will rapidly be made aware of the great need for much more investigation in this important field before many of the most fundamental questions can be answered. The author has done a great service, however, in setting down the presently known material, and the volume should be of value to investigators in the field of vascular disease. T. D.

UNRUHE, ZWANG, ANGST. BY DR. POUL BJERRE. Pp. 148. Munich: J. F. Lehmanns Verlag, 1955. Price, DM 13.

DR. BJERRE, the well known Swedish psychotherapist, has developed what he considers his own philosophy of psychotherapy. However, this, as many of his preceding books, offers little of interest to the methodically trained medical psychotherapist. Some of his stories are dramatic but they are not in the medical sense case histories nor is there a worthwhile contribution to the problem which the author states on page 11: The development of neuroses is connected with the development of character.

One will not disagree in this post-Freudian age that the treatment of neuroses is confronted with resistances stemming from the past; there is no quarrel either with the statement: The physician must help nature's own curative tendencies. Over and beyond this, there is not much the American physician could derive from the book. W. E.

ADVANCES IN INTERNAL MEDICINE, VOLUME VII, 1955. Edited by WILLIAM DOCK, M.D. AND I. SNAPPER, M.D. Pp. 311; 27 ills.; 11 plates. Chicago: The Year Book Publishers, Inc., 1955. Price, $8.50.

As has been true with past volumes in this series, the editors have selected a series of topics which are timely in the sense that definite progress has been made and in which there is need to bring together in a concise form the present status of knowledge. The subjects discussed are: Pathogenesis and Treatment of Renal Lithiasis (A. J. Butt), Hepatic Coma (C. S. Davidson), The Pathophysiology of the Pancreas (D. A. Dreiling and H. D. Janowitz), Clinical Significance of Serum Mucoproteins (E. M. Greenspan), Advances in Physiology of Clinical Disorders of the Adrenal Cortex (J. W. Jailer), Diseases of the Pericardium (V. A. McKusick and A. McG. Harvey), The Nephrotic Syndrome (J. B. Squire), and Applied Pulmonary Physiology (D. J. Stone). Simply reading these titles was enough to stimulate the reviewer's intellectual digestive juices, and he found that the partaking of the meat in each was every bit as satisfying and worthwhile as had been anticipated. It is a volume highly to be recommended to all physicians. T. D.

CARDIAC DIAGNOSIS: A PHYSIOLOGIC APPROACH. BY ROBERT F. RUSHMER, M.D., Associate Professor of Physiology and Biophysics, University of Washington Medical School. Pp. 447; 239 ills. Philadelphia: W. B. Saunders Co., 1955. Price, $11.50.

THIS book emphasizes the mechanisms, described in terms of physical and physiologic principles, by which disease processes produce various signs and symptoms. The book

bridges the hiatus between pure physiology (and anatomy) on the one hand and clinical cardiology, relying much on characteristic empirical patterns of signs and symptoms, on the other hand. The first part discusses the functional anatomy of cardiac contractions, the functional characteristics of the systemic and pulmonary circulation, and the circulatory response to arising. The second part deals with the principles of peripheral vascular control, the regulation of cardiac output, and with the factors that determine stroke volume. The third part is devoted to cardiac reserve and to the etiology of congestive heart failure. Part IV deals with methods of cardiac diagnosis: measurement of pressure, size and configuration of the heart, estimation of cardiac output, and electrocardiographic interpretation. The application of fundamental concepts and diagnostic methods to clinical problems constitutes Part V, presenting several categories of heart disease, myocardial ischemia, myocarditis, valvular disease, congenital heart disease and possible heart disease. The illustrations are excellent and didactic and the legends render them independent of the text. The references refer chiefly to more recent publications and provide a point of departure for further reading.

The author is not dogmatic and it is refreshing to see him direct attention to deficiencies in current knowledge. The book is well recommended. H. R.

NEW BOOKS

Psychotherapy and Counseling. By L. K. Frank, Rollo May and 46 other researchers. Edited by Roy Waldo Miner. Ann. New York Acad. Sci., **63**, Art. 3, pp. 319–432. New York: New York Academy of Sciences, 1955. Price, $3.50.

This is a collection of short statements from representatives of various disciplines who met in a conference to share ideas. The purpose of the conference was to describe the current common and accepted practice by which each of these professions seek to meet those human needs that can be helped by psychotherapy and counseling, however designated, and to decide also the particular training now being provided.

These disciplines met in commissions and the resulting consensus from each commission appears as a statement by the chairman. Represented were medicine, psychology, social work, counseling and guidance and the ministry. There is some discussion added to supplement some of the commissions' statements.

Lawrence K. Frank emphasises in a summary that each group considered itself operating as a responsible social agent to make operational the cherished belief in the worth of individual personality. Each group accepted the fact that further training and clinical experience was needed beyond obtaining a degree. He stresses a need for unlearning certain things as well as learning others. He urges the need for being multidimensional in thinking and urges all professions to become increasingly concerned with human personality in all its dimensions. O. E.

Polycythemia. By John H. Lawrence, M.D., D.Sc., Director, Donner Laboratory, and Professor of Medical Physics, University of California. Pp. 136; 38 ills., and 1 color plate. New York: Grune & Stratton, Inc., 1955. Price, $5.50.

This splendid monograph is based on more than 20 years of experience which the distinguished author has had with polycythemia. Based on studies dealing with 303 patients, Lawrence has considered primary and secondary forms of the disorder, as well as relative polycythemia, from the clinical, laboratory, and therapeutic standpoints.

Anyone interested in reading a comprehensive, authoritative account of polycythemia and its management will find it in this small volume. C. Z.

Transactions of the 14th Conference on the Chemotherapy of Tuberculosis: Veterans Administration: Army: Navy. Pp. 556; illustrated. Washington: Veterans Administration, 1955.

This volume consists of some 59 papers on various aspects of tuberculosis which were presented at the meeting held in Atlanta, Georgia, on February 7 through 10, 1955. In addition to the original papers, there are included articles read by title as well as many comments and other pertinent discussions on the material presented. Although the reports are often fragmentary, the transactions will be of interest to workers in the field of tuberculosis for whom the volume is primarily intended. C. Z.

Varicose Veins. By R. Rowden Foote. Pp. 110; 29 ills. Chicago: Henry Regnery Co., 1955. Price, $2.25.

This small volume is one of the Modern Health Series. It is designed to acquaint the general public, and particularly that large segment suffering from varicose veins, with authoritative information on this disorder. The language is simple and the necessary medical terminology employed is explained in a brief glossary. The illustrations and figures are well chosen. Physicians may profitably recommend this book to their patients with venous disease of the extremities. N. L.

The Year Book of Medicine (1955–1956 Series). Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D. Tinsley R. Harrison,

M.D., FRANZ J. INGELFINGER, M.D., AND PHILIP K. BONDY, M.D. Pp. 711; 121 ills. Chicago: Year Book Publishers, Inc., 1955. Price, $6.00.

THE most recent volume of this series of Year Books covers articles published in journals during the period May, 1954, to May, 1955. Although a few papers of importance have apparently been overlooked, the editors have again performed a valuable service in abstracting the medical literature in their respective fields of interest. Internists will find much important information conveniently presented in this small volume. C. Z.

Hypnotic Suggestion. BY S. J. VAN PELT, M.B., B.S. Pp. 95. New York: Philosophical Library, 1956. Price, $2.75.

THIS is a small book giving the theory and technique of hypnosis in an abbreviated but sufficiently useful form of 95 pages including index. The author additionally discusses psychoneurosis regarding them as being in the nature of a posthypnotic suggestion. By a series of six or more hypnotic inductions the author feels he can get successful results in breaking up the effects of anxiety provoked in the mind of the patient and free him from his neuroses. He gives 12 brief case histories to show his procedure and results. These cases range from asthma to alcoholism, from hysteria to migraine. There is a list of references. O. E.

Biology of Poliomyelitis. BY KARL HABEL AND OTHERS. Edited by ROY WALDO MINER. Pp. 328; illustrated. New York: New York Academy of Sciences, 1955. Price, $5.00.

THIS publication contains the papers presented at the conference on the Biology of Poliomyelitis held in New York in January, 1955. The papers are grouped in five sectins: 1) Poliomyelitis Virus and Methods for Its Study, 2) Susceptibility of Cells and Organisms to Poliomyelitis, 3) Poliomyelitis Virus Variation, 4) Poliomyelitis and the Community, and 5) Immunization against Poliomyelitis. This collection of papers is extremely valuable for the person interested in the virus of poliomyelitis and its epidemiology. W. N.

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